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ANNALS OF THE RHEUMATIC DISEASES

CONTENTS

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ARTHROMYODYSPLASIA CONGENITA

SIMULATING THE ARTHRITIC MANIFESTATION OF "RHEUMATOID DISEASE"

BY

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(RECEIVED FOR PUBLICATION OCTOBER 6, 1953)

"Rheumatoid disease" in its acute or chronic form with systemic or local manifestations may simulate many diseases in general medicine. Local manifestations may resemble many specific arthritides and bony and muscular lesions with secondary joint involvement (Ellman, 1947; Ellman and Ball, 1948), and two cases of a chondro-osseous dystrophy, which had been regarded as an arthritic manifestation of "rheumatoid disease", have already been reported (Ellman, 1949).

The purpose of this paper is to give an account of a unique case of so-called "amyoplasia congenita" or "arthrogryposis multiplex congenita", which we, for reasons to which we shall refer in the discussion, prefer to designate "arthromyodysplasia congenita". This condition occurred in a roadsweeper aged 40, who was initially referred as a case of "rheumatoid arthritis". The flexion deformities of fingers, wrists, elbows, and knees, and the fixation of these joints, give the impression of a fibrous ankylosis, hence the terms "multiple articular rigidity" and "arthrogryposis multiplex". As we shall show, the symmetrical joint immobility and flexion deformity are never associated with any inflammatory change, but depend upon some congenital developmental defect, probably associated with a dysplasia of certain groups of muscles with changes occurring in and around the joints.

Case Report

Male, aged 40, single, roadsweeper, was admitted to the Rheumatism Unit at St. Stephen's Hospital as a possible case of "rheumatoid arthritis". At the time of admission he was complaining of pain and stiffness in the knees, ankles, and toes, together with occasional aching of the shoulders and upper limbs in general for the past 2 months. In addition to his polyarthralgia he had been complaining of some breathlessness on exertion.

His past history showed that ever since he could remember he had had several severe joint deformities, in fact since the age of 2½ years when he had attended the paediatric department of a London hospital for an apparently congenital condition of his limbs. He had been under their supervision until he had reached the age of 16, but in spite of these very marked deformities he had worked as a roadsweeper until 7 weeks before admission to hospital. There was no relevant family history.

Clinical Examination.—Pupils equal and reacted to light and accommodation; disks healthy; no evidence of disease clinically in heart, lungs, abdomen, or central nervous system. Blood pressure 130/80. No clinical evidence of anaemia. No lymphadenopathy, hepatomegaly, or splenomegaly.

X-Ray Examination of the heart was within normal limits.

Electrographic Examination normal.

Locomotor System.—Severe limitation of movement in elbow joints which were almost fixed at a right angle. Flexion deformities of hands and wrists (Fig. 1). No abnormality of the spine. Hip joints considerably restricted in range of movement. Knees similarly restricted, the right one being painful. Ankles also limited to a few degrees of movement in the middle range (Fig. 2, overleaf). Joint lesions all of a secondary degenerative nature.

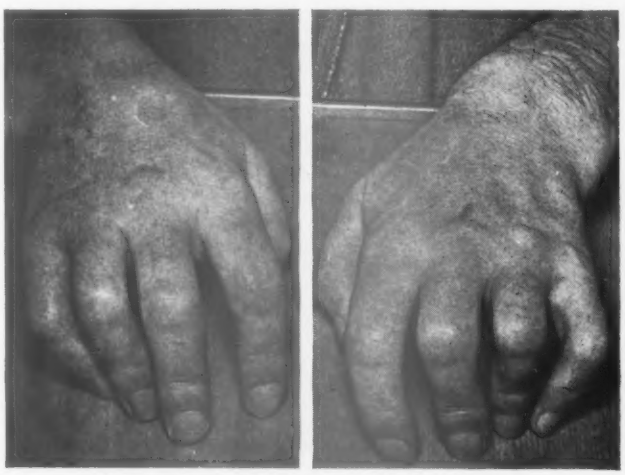

Fig. 1.—Flexion deformities of hands and wrists.

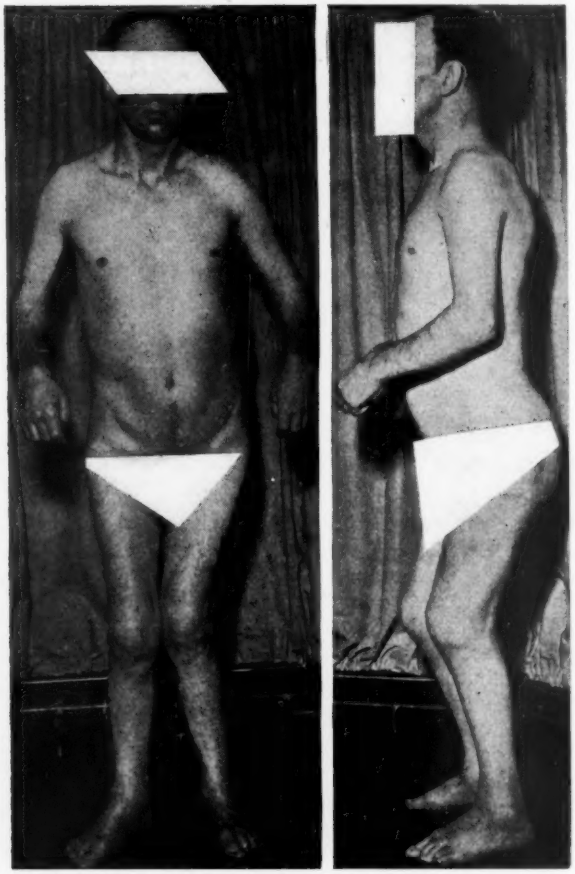

Fig. 2.—Body posture (anterior and lateral views), showing flexion deformities in upper and lower limbs.

Fig. 3.—Secondary degenerative joint changes involving ankles.

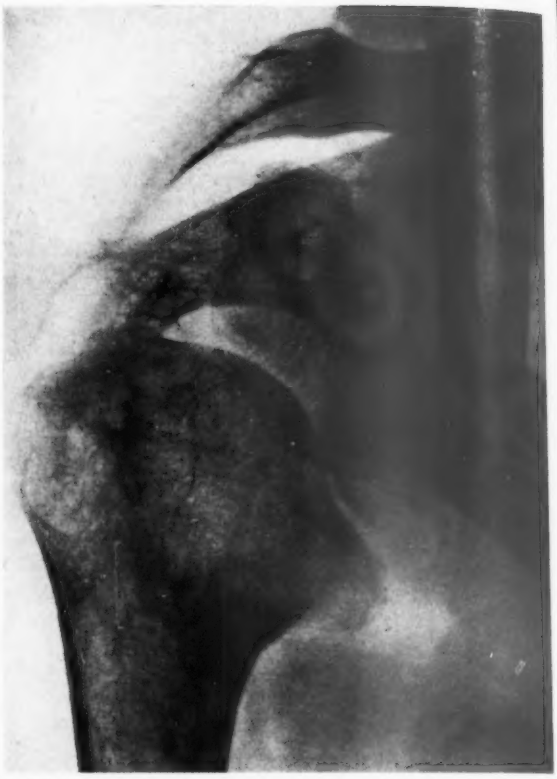

Fig. 4.—Right shoulder, showing presence of several loose bodies.

Range of movement in the joints:

Elbows:	Right	Extension limited to 85°. Flexion full, 150°.
	Left	Extension limited to 80°. Flexion 80-135°.
Shoulders:	Both	Abduction to 60°. Internal rotation full. External rotation limited. Flexion to 90°.
Wrists:	Both	Dorsiflexion 10°. Plantar flexion 70°.
Hands:	All fingers flexed to 70°.	
Knees:	Right	Flexion 80°. Extension 150°.
	Left	Flexion 70°. Extension 150°.
Ankles:	Both	Dorsiplantar flexion limited. Range 30°.
Hips:	Both	Flexion 50°. Abduction to 17 in. between feet when standing on one. Abduction to 20 in. between feet when both abducted.

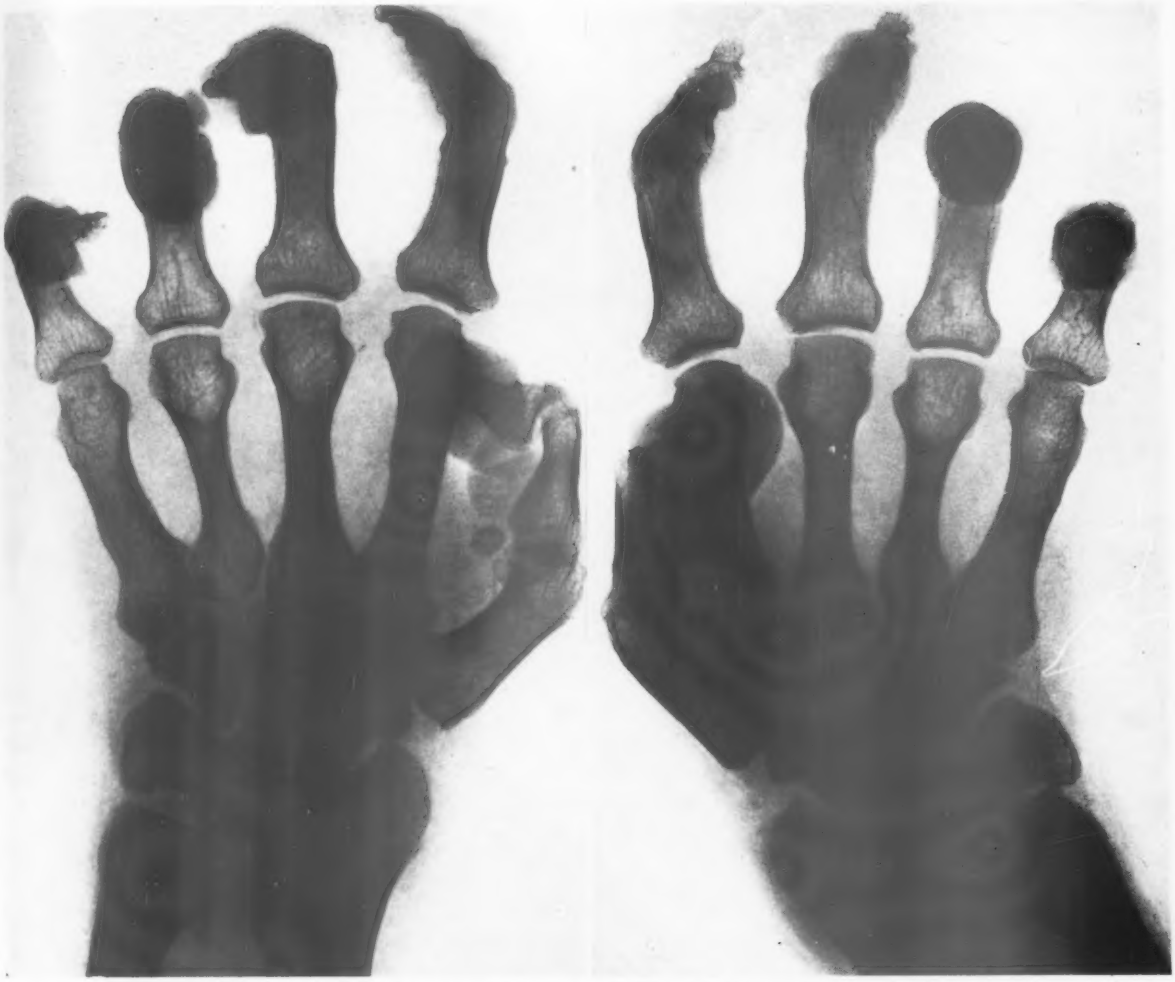

Fig. 5.—Hands, showing short metacarpals and flexion deformity with secondary degenerative changes.

X-Ray Examination confirmed the clinical findings and showed degenerative changes in all joints, especially the knees. These changes were regarded as secondary to an older lesion which had occurred during the period of growth. A noteworthy radiological feature was the existence of several loose bodies in the shoulders and elbows. There was a generalized trabeculation of the bone with some generalized osteoporosis of the epiphyseal ends. The bones showed evidence of a very uneven growth. The metacarpals were short. The dorsilumbar spine showed no abnormality. In the elbows the upper ends of the radii were ankylosed to the ulnae, and above each and apparently attached to it was a body resembling a radial head (Figs 3, 4, 5, and 6).

Pathological Investigations:
Blood-count: normal.
Blood sedimentation rate (Westergren): normal.
Blood urea, plasma uric acid, plasma proteins: all within limits of the normal.
Alkaline phosphatase: 17·2 units per 100 ml.
Liver function tests: normal.
Wassermann reaction and Kahn test: negative.

Discussion

This case of amyoplasia congenita (Sheldon, 1932) or arthrogryposis multiplex congenita (Stern, 1923) is apparently the only case yet described in a patient as old as 40, still actively employed in manual labour. (Albeaux-Fernet and Weissenbach, 1952, described a case in a man, aged 23, observed from birth.) In regard to terminology we prefer the recently suggested name, arthromyodysplasia congenita (Sürder, 1952). It is impossible to say that the joints are affected secondarily to the muscles, or that the muscles are affected secondarily to the joints. It is more likely to be a primary developmental abnormality of both the muscles and the joints. Many other names for the disease have been

Fig. 6.—Pelvis, showing secondary degenerative joint changes in hips.

employed (see Parkes Weber, 1947a, b; Kallio, 1948; Keizer, 1949; and Hagberg and others, 1952). The disease occurs in widely different forms and degrees, and in combination with various other developmental abnormalities or syndromes.

Sheldon (1932), in his paper on amyoplasia congenita, recorded the case of a child, aged 2 yrs, with congenitally rigid arms and legs, associated with aplasia of certain muscle groups. He stated that under the names "multiple congenital articular rigidity" and "arthrogryposis multiplex congenita" a rare but well defined condition had been described:

> The characteristic features consisted of immobility of one or more joints of the limbs, generally symmetrical in distribution, and dating from intrauterine life. The immobility may be absolute, or movement may be severely limited. The fixation of the joints has the clinical appearance of fibrous ankylosis, but evidence of inflammatory change to account for this is absent, and it would appear more probable that the condition depends primarily upon some developmental defect. In this connection the incomplete development, or even entire failure of development of certain groups of muscles in the limbs, which has been recorded in cases specifically examined from this point of view, has been a striking feature.

Sheldon thought that the most likely explanation was that the initial defect was a developmental aplasia or dysplasia of certain groups of limb muscles, secondary developmental changes occurring in and around the joints leading to the clinical picture of fibrous ankylosis. This does not signify that congenital abnormalities may not sometimes be caused by faulty position, fold, bends, etc., *in utero*.

Amongst recent writers using the term arthro-

gryposis multiplex congenita are Kallio (1948), Keizer (1949), Metcalfe (1951), Albeaux-Fernet and Weissenbach (1952), and Hagberg and others (1952); Jeune and Bruel (1950) prefer the name amyoplasia congenita.

Middleton (1934) prefers to call the condition myodystrophia foetalis deformans. He draws an analogy between it and the muscular dystrophies of post-natal life. He says it was first described by Otto (1841).

In 1929 Sir Heneage Ogilvie and his resident medical officer, F. J. Lees, showed Parkes Weber some cases at St. Vincent's Orthopaedic Hospital (Parkes Weber, 1947a, b). In Ogilvie's series the occurrence of associated developmental abnormalities was noteworthy. Thus, in one of the female patients, there was a urachus abnormality, the urinary bladder reaching nearly up to the umbilicus. Another patient had a brother or sister affected with meningocoele or encephalocoele, and another seems to have had a fellow sib with cleft palate.

Dr. D. M. Greig, of Edinburgh, kindly directed our attention in 1929 to investigations by Hutt and Greenwood (1929) on embryonic mortality in the fowl, and chick monsters in relation to embryonic mortality. Greig wrote to one of us (F.P.W.) as follows:

> In addition to cranial and facial deformities there are included congenital malformed limbs, thickened and flattened tarsometatarsus, unilateral absence of muscles, and absence of one or two toes. The joints are bent on account of the muscular anomalies and many cases of twisted feet and toes are mentioned as occurring, but are not described.

Greig himself had seen the chicks and had no doubt of the congenital distortions of the limbs.

Rocher (1913), in his comprehensive account of the disease referred to by Sheldon, pointed out that first-born children are not especially affected and that in his cases there was no familial or hereditary tendency. He directed attention to abnormalities of the hands and feet, notably flexion of the fingers, claw-hand, and club-foot; shortening of the flexor tendons of the fingers has been reported as in Volkmann's ischaemic contracture, flexion of the fingers being more easily performed when the wrists are also flexed. The patella is often abnormal, being displaced, small or even absent.

> The muscles never show a reaction of degeneration, so that the muscular atrophy is probably not of nervous origin, but the reactions to faradism and galvanism are diminished or absent, indicating hypoplasia or complete aplasia of muscle. There are no sensory or trophic changes. The tendon reflexes are naturally difficult to obtain, but when present, they are not increased.

The children in his cases were of normal intelligence. He also noted the thickened appearance of the subcutaneous tissues obliterating the normal bony markings in parts of limbs, but in a case reported by Magnus (1903) this subcutaneous thickening was absent, and the muscular aplasia was so great that the child appeared to be simply skin and bone. Rocher stated that there might be some shortening of the affected limb or segment of a limb. Amongst associated conditions there might be ankylosis of the mandible and some vertebral stiffness or scoliosis. A later paper (Rocher and Ouary, 1930) recorded the case of a girl, aged 3 months, with fixation of the legs in extension and double talipes, associated with several malformations of the lumbar vertebrae and aplasia of the sacrum. According to these authors there may be abnormality of the synovio-capsulae arrangement of joints.

Moncrieff and Wiles (1934), observing that Middleton (1934) had noted the resemblance of amyoplasia congenita to a sporadic disease occurring in sheep, wrote:

> Should the two prove to be identical, it will be of great interest, because Fraser Roberts (1926, 1929) has been able to show by selective breeding that in sheep the condition depends upon the homozygous state of an autosomal recessive factor.

Edwards (1938), demonstrating an infant with "webbing of the lower limbs, associated with congenital bilateral contractions of flexor muscles of elbow and wrists" (which we suppose to be allied to arthromyodysplasia congenita), referred to the question of such "webbing" representing an atavism analogous to the webbed wing of a bat, and observed that similar folds are seen in the neck of a chimpanzee. He said that Bruns and Kredel (1890) maintained that the conditions of webbing owed its origin to misplaced and abnormal muscular developments, bridging the flexor surfaces of joints and displacing the overlying skin in web-like formation. Traces of muscular tissue are often encountered between these skin folds.*

In regard to associated developmental abnormalities, an interesting case was described by Herson (1947). The patient was a woman, aged 61 years, who in addition to amyoplasia congenita had a condition of hyperostosis frontalis interna. A more complicated case was that of a boy, aged 14 years, demonstrated by Williams (1948), in which there was maldevelopment of the osseous, muscular, and subcutaneous tissue, with central nervous system dysfunction.

Various questions arise from the consideration of arthromyodysplasia congenita:

* In this connection compare also scattered literature on "Brevicollis", "Klippel Feil Syndrome", and "Webbed Neck".

Perhaps some abnormalities of the hands, such as congenital camptodactylia,* with or without webbing (compare Parkes Weber, 1938, 1947a) might be regarded as minor varieties of arthromyodysplasia congenita. We would instance especially the case of a man, aged 47 years, with congenital or early developmental camptodactylia of both little fingers and considerable atrophy (or more probably hypoplasia) of the intrinsic muscles of the hands, who had likewise had a kind of facial telangiectasia of the Rendu-Osler type for as long as he could remember (Parkes Weber, 1938?).†

Should the term arthromyodysplasia congenita be used to include cases of localized muscular aplasia of the whole part of the pectoralis major muscle, of certain muscles of the abdominal wall, of bigger congenital defects of the thoracic or abdominal walls, and of fibrous dysplasia of a sternomastoid muscle?

May not some post-natal cases of local muscular dystrophy be regarded as representing a deferred arthromyodysplasia congenita?

Is there a condition of developmental dysplasia of subcutaneous tissue analogous to, and sometimes associated with, arthromyodysplasia congenita?

Middleton (1934) discusses the relation of arthromyodysplasia congenita to congenital tibial kyphosis (congenital angulation of the tibia) and to congenital high shoulder (congenital elevation of the scapula, "Sprengel's shoulder"). Congenital hypoplasia or aplasia of the patellae have also been recorded in association with various types of congenital ectodermal defects (Parkes Weber, 1929).

The remarkable case described by Batten (1904) as "myositis fibrosa" might conceivably be regarded as a rare or even unique variant of arthromyodysplasia congenita. The curious case described by Huber and others (1951) was apparently a chance combination of arthromyodysplasia congenita with a hypervitaminosis D2 in the foetus, the latter condition being due to the mother having taken large doses of vitamin D2 throughout her pregnancy.

As stated above, we prefer the name arthromyodysplasia congenita (Sürder, 1952). Moreover, we regard the term "dysplasia" as preferable to "aplasia" in most of the recorded cases. Sürder points out that, though there is abundant evidence of the occurrence of familial congenital contractures of joints in animals, these contractures are rare in human beings. In solitary cases, without any evidence of familial or hereditary tendency, neither exogenous causes, nor new mutations can be absolutely excluded.

There seems to be no evidence that the disease is ever due to intra-uterine toxaemia or infection due to an infectious disease in the mother, such as rubella at an early stage in the pregnancy.

Confusion with changes due to the rheumatoid or osteo-arthritic type of arthritis may occur, but as the foregoing shows, this should create no real problem.

In regard to *treatment*, little can be said. Though most authors mention that no treatment has been found of any use, Metcalfe (1951) mentions as useful Sir Thomas Fairbank's advice in the case of infarcts to stretch the tight tissues gently two or three times a day.

Summary

A case of arthromyodysplasia in a man, aged 40, is described. The causation, symptomatology, nomenclature, and literature of the disease are discussed, together with its not infrequent association with other developmental abnormalities. The possible confusion of this condition with rheumatoid disease is noted.

Various minor varieties of congenital (or early developmental) contracture deformities of the extremities deserve to be regarded as possible slight cases of arthromyodysplasia congenita. Foremost amongst these are examples of congenital camptodactylia with or without "webbing" and "hypoplasia" of the corresponding muscles. There is no reason why such slight developmental abnormalities should hinder the attainment of ordinary longevity.

* Regarding the difference between congenital and acquired camptodactylia (see Parkes Weber, 1947a), the term "camptodactylia" (bent fingers) was introduced by Professor L. Landouzy (1885). Congenital or early developmental camptodactylia seems to be an abnormality of development—a minor localized variety of arthromyodysplasia congenita, whereas acquired camptodactylia appears to be a variety of ordinary Dupuytren's contracture.

† Dr. J. W. Rae and Dr. W. E. Alderson have kindly told us of a somewhat analogous case of early developmental camptodactylia in a man, aged 27 years, associated with multiple superficial naevi, only in their case the naevi were of angiomatous and pigmented, hairy types instead of Oster's telangiectatic type. The camptodactylia which affected all his fingers and toes had been noticed at about age 6, and the multiple naevi at age 18 (Alderson, 1953).

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Arthromyodysplasie congénitale simulant les manifestations arthritiques de la "maladie rhumatismale"

RÉSUMÉ

On décrit un cas d'arthromyodysplasie chez un homme de 40 ans. On en discute l'étiologie, la symptomatologie, la nomenclature et la littérature, ainsi que le fait que cette maladie est souvent associée à d'autres anomalies évolutives. On note qu'elle prête à confusion avec la maladie rhumatismale.

De différentes variétés mineures de contracture avec déformation congénitale (ou acquise précocement) des extrémités devraient être considérées comme des cas probables d'arthromyodysplasie congénitale légère. Un des meilleurs exemples de tels cas est la comptodactylie congénitale, avec ou sans palmure, et "hypoplasie" des muscles correspondants. Il n'y a pas lieu de croire que ces anomalies évolutives légères affectent la probabilité de survie.

Artromiodisplasia congénita simulando las manifestaciones artríticas de la "enfermedad reumática"

SUMARIO

Se describe un caso de artromiodisplasia en un hombre de 40 años. Se discute su etiologia, sintomatología, nomenclatura y literatura, así como el hecho de que esta enfermedad se ve frecuentemente en asociación con otras anomalías de desarrollo. Se nota la posibilidad de confusión de este disturbio con la enfermedad reumática.

Diferentes variedades menores de contractura con deformidad congénita (o evolutiva precoz) de las extremidades deberían considerarse como casos probables de artromiodisplasia congénita ligera. El primer lugar entre ellos ocupan los ejemplos de comptodactilia congénita, con o sin palmeadura, y "hipolasia" de los músculos correspondientes. No hay razón de pensar que estas anomalías evolutivas ligeras afecten la probabilidad de superviviencia.

PULMONARY LESIONS OF DISSEMINATED LUPUS ERYTHEMATOSUS

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 28, 1953)

Two patients were seen recently with distinctive pulmonary parenchymal lesions due to disseminated lupus erythematosus. The more classic manifestations such as skin lesions, carditis, polyserositis, and nephritis, were not at first apparent, but typical L.E. cells were demonstrated in the peripheral blood of both patients, and the diagnosis was confirmed by further study. This prompted us to review the published descriptions of the pulmonary manifestations of this disease and to observe in our patients the clinical effects of adrenocortical hormone therapy upon the lung lesions.

Previous Descriptions of Lung Lesions

Intercurrent pneumonia was described by Kaposi (1872) in his original account of the visceral lesions of lupus erythematosus. Many reports have since mentioned the frequency of pulmonary findings, particularly in the end stages of the disease. The serosal inflammation which results in acute fibrinous pleuritis, pleural effusion, and chronic fibrous pleuritis, has long been accepted as a distinctive feature, but the recognition of a specific pulmonary parenchymal lesion has been less certain, both at the bedside and at autopsy. Many accounts of visceral lesions fail to mention the lung parenchyma or to distinguish between a primary parenchymal lesion and a secondary infective pneumonia. Full consideration has not been given to the possibility that the frequent bouts of "broncho-pneumonia" suffered by these patients may be due to an underlying alteration of the respiratory membrane rather than to the debility of prolonged illness.

The concept of disseminated lupus erythematosus as a systematic alteration of the collagen ground substance was advanced by Klemperer, Pollack, and Baehr (1941), who referred to "long bouts of waxing and waning, migrating bronchopneumonia" characterizing the clinical course of their cases. At autopsy, they found that this pneumonia was "in no way specific", and the only lung lesion of systemic implication which they described was fibrinoid change in the small pulmonary arteries of a single case. This paucity of pulmonary parenchymal findings is the more striking in view of their detailed description of the lesions in the heart, kidney, spleen, lymph nodes, and serous membranes.

Rakov and Taylor (1942) appear to have been the first to focus particular attention upon the pulmonary parenchyma in disseminated lupus. They described a patient in whom pulmonary consolidation was the dominant finding from the onset of symptoms to death 8 months later. On gross examination both lower lobes were found to be atelectatic, although their bronchi were open. The microscopic picture was that of a chronic low-grade interstitial pneumonitis which had progressed to atelectasis. The authors called attention to a patient reported by Osler (1904) in his descriptions of the visceral manifestations of the erythema group of skin diseases, and to another described by Tremaine (1934) as subacute Pick's disease; both were probably instances of protracted primary pulmonary lesions in lupus erythematosus.

Foldes (1946) described the clinical and pathological findings in a patient with disseminated lupus erythematosus who died of respiratory failure due to massive atelectasizing pneumonitis.

Teilum (1946) delineated what he considered to be the specific morphological characteristics of the pulmonary lesion of lupus erythematosus. He stated that the histological characteristics of the lung lesion serve as prototypes of the various stages of tissue injury which occur in this disorder. He described a focal allergic pneumonia which varied in intensity in different parts of the lung but was most pronounced just beneath the pleura. He also recorded the presence of fibrinoid thread-and-band-like masses in the interalveolar septa, areas of complete necrosis of the septal wall, accumulations of histiocytes, organization of areas of fibrinoid necrosis to form small granulomata, areas of fibrosis, and pronounced allergic vascular changes.

Baggenstoss (1952) stated that there is no pathognomonic pulmonary parenchymal lesion, but he and his colleagues have also observed the chronic interstitial atelectasizing pneumonitis described by Rakov and Taylor, and by Foldes. In addition, Baggenstoss described a "peculiar basophilic mucinous oedema of the alveolar walls and of the peribronchial and perivascular tissues"; he noted that these lesions are quite separate from the ordinary pyogenic and fibrinous types of bronchopneumonia which may complicate the disease.

That this differentiation may be difficult clinically can

be inferred from a review by Tumulty and Harvey (1949). Abnormal pulmonary findings had been recorded at some time during the illness of nineteen of 32 patients autopsied at the Johns Hopkins Hospital, but the lungs of only three showed "classical lesions of this disease", and these were patients with minimal clinical evidence of pulmonary involvement. In one, physical examination of the chest was negative, but *x* rays revealed a diffuse non-tuberculous type of infiltration similar to that found in our own second case. This infiltration, on histological examination, was found to consist of "focal haemorrhages and focal alveolar exudate with organization, thought to be typical of the changes seen in rheumatic fever, periarteritis nodosa, and sulphonamide hypersensitivity".

Sante and Wyatt (1951), in a discussion of the radiological characteristics of antigenic pneumonitis, stated that there was "little, if any, indication of lung involvement" in lupus erythematosus until just before the final stages of the disease. However, Thorell (1952) described in detail what he considered to be characteristic chest-film findings in disseminated lupus erythematosus. Small, often bilateral pleural effusion and irregular pleural thickening were most common, and these were frequently accompanied by parenchymal changes consisting of mottled and streaky consolidation, mostly subpleural in location and usually confined to the bases. Thorell suggested that this combination of pleural and parenchymal changes should warn the radiologist of the diagnostic possibility of disseminated lupus. In his series there were no films of pulmonary parenchymal changes without accompanying pleural changes, massive pulmonary consolidation, or atelectasis.

Thus it is apparent that while pulmonary lesions in disseminated lupus are frequent, they are often atypical and difficult to evaluate. It may be that the lungs are as common a site of primary involvement as the heart, kidneys, or serous membranes. This is not definitely known because of the tendency in the past for clinicians to label parenchymal lesions as "pneumonia" without further qualification, and because the histological lesion is still in the process of identification by the pathologist. Primary involvement may occur as asymptomatic, diffuse infiltrates discoverable only by *x*-ray examination, or, on the contrary, it may present as a massive pulmonary consolidation or atelectasis. Perhaps the most common pattern is that of patchy, shifting areas of pneumonitis, usually at the bases and associated with a pleural reaction. It would seem important to recognize such lesions clinically, since their significance and treatment are so different from that of a secondary bronchopneumonia. The two cases described below illustrate some features of their clinical behaviour.

Case Reports

Case 1, a white marine engineer, aged 44, was referred to this hospital from a public health clinic in October, 1952, with a diagnosis of probable primary atypical pneumonia.

History.—He stated that he had been ill since February, 1952, when he developed "the shingles". This was soon followed by weakness, generalized muscle aching, numbness, and tingling of hands and feet in the morning, coughing, shortness of breath, and a pleurisy-like pain, which spread across his lower anterior chest and into his left shoulder. He became febrile, failed to respond to intramuscular injections of penicillin, and, in late April, 1952, he entered a hospital. His temperature on admission was 103·5° F. He was short of breath and had a cough productive of frothy, mucoid sputum, a bilateral pleurisy, and bilateral crepitant basilar rales. A chest film (Fig. 1) revealed "bilateral bronchopneumonia" with evidence of pleural exudate. An electrocardiogram disclosed "marked ST segment shift suggestive of the acute stage of pericarditis". One examiner's note mentioned a "low white count". The patient continued febrile and severely ill despite the administration of penicillin, aureomycin, terramycin, and chloromycetin. He lost 60 lb. in weight within 6 weeks. Sputum examination for bacteria, fungi, malignant cells, and eosinophils, test for cold agglutinins, and a coccidiodin skin test were all negative. Blood cultures, febrile agglutinins and a heterophil agglutination test were negative. A bone marrow examination with a search for L.E. cells was reported as negative, but the type of preparation made was not stated.

Although a diagnosis was not established, ACTH therapy was initiated about June 1, and he received four injections daily of an unknown amount for 25 days. He became afebrile, gained 20 lb. and noted marked relief of his chest pain. A progress chest film (Fig. 2) disclosed "partial resolution of the bilateral pneumonitis". He was then sent home on one daily injection of ACTH, but within 3 weeks the fever and other symptoms returned, and in mid-July he was admitted to another hospital. His pulse and respirations were rapid on admission, but physical examination of his lungs was reported as negative. A chest *x* ray showed what was interpreted as a low grade pneumonitis at the left base with a suggestion of a low grade pleural reaction. A white blood cell count was 5,600 per cu. mm. One of several urine analyses revealed 10-20 red blood cells per high-powered field. An unknown amount of ACTH was then given until the end of July, and the patient was discharged from the hospital at the end of August with a diagnosis of primary atypical pneumonia. A chest film prior to discharge (Fig. 3) was essentially unchanged from the admission film. During the next 6 weeks he was followed as an out-patient, but when his original symptoms of pleurisy, breathlessness, weakness, and numbness and tingling of the extremities again became worse, he was referred to this hospital for further study.

Examination.—The patient was an alert, well-developed, middle-aged, white man (height 6 ft. 2 in., weight 180 lb.). Temperature 99·5° F.; pulse 90 and regular; blood pressure, 94/70. Respiration rapid and restricted by sharp, lower left anterior chest pain radiating into the left shoulder on attempted deep inspiration. Head and neck normal. Tactile fremitus and percussion resonance impaired over both lung bases. Bilateral, crepitant, late inspiratory rales, persisting after cough, heard at both bases. PMI felt in fifth intercostal space at anterior axillary line. Heart sounds quiet, with a soft basal systolic murmur. Abdominal and neurological findings within normal limits. Slight periarticular swelling and tenderness of right fourth metacarpophalangeal joint

were noted. Skin clear except for seborrhoeic macular rash over "V" area of chest.

Laboratory Data:

Haemoglobin, 14·4 g.; white blood cell count, 4,350; differential count, 74 per cent. neutrophils, 21 per cent. lymphocytes, 3 per cent. monocytes, 1 per cent. eosinophils, 1 per cent. basophils.

Sedimentation Rate: 33 mm./hr (Wintrobe uncorrected).

Urine analysis: specific gravity, 1·014-1·020; albumin, negative to a trace; sugar, negative; sediment, occasional to many white blood cells, no red blood cells, negative tests for occult blood.

Cardiolipin and Kahn tests: negative.

Blood chemistry: blood urea nitrogen, 13 mg. per cent.; cephalin-cholesterol flocculation, 1+; thymol turbidity, 3 units; total serum proteins, 6·6 g. per cent.; albumin, 3·6 g. per cent.; globulin, 3·0 g. per cent. Electrophoretic analysis of serum proteins: elevation of α 2 and γ globulins.

Radiology.—Chest film on admission disclosed prominent left ventricular border, considerable mottling throughout right lung field, particularly at base, and some mottling at left base. This appearance suggested a resolving bilateral pneumonitis.

Electrocardiogram.—Within normal limits.

Biopsy.—Kveim test and random muscle biopsy for evidence of sarcoid (Myers and others, 1952) both negative.

L.E. Cell Preparation (made by defibrination of the patient's peripheral blood immediately following withdrawal and preparation of smears of the buffy coat after 2 hrs' incubation at room temperature) revealed large masses of L.E. rosettes and many typical L.E. cells.

Therapy.—The patient was confined to bed with his head elevated for comfort. Rapid, shallow breathing persisted, as did his complaints of pleuritic pain and numbness and tingling of his hands and feet. Walking to the bathroom left him breathless. He did not cough, and auscultation of the lungs revealed only a few crepitant rales at the bases. There was evening fever to about 100° F. After 3 weeks' symptomatic therapy he was unimproved. Therefore, in view of the positive L.E. cell test, ACTH therapy was started. He received 10 i.u. ACTH (Armour) daily by intravenous drip in 1,000 ml. 5 per cent. dextrose in water, given over 16 to 18 hours (Mandel and others, 1951). Within 24 hours he felt better and his temperature returned to normal. During the first week of therapy his numbness and tingling vanished, and he was able to breathe deeply with only a twinge of pleural pain. Within 2 weeks his sedimentation rate was normal. On the 17th day of treatment the dosage of ACTH was reduced to 5 mg. daily because a pronounced Cushing effect had been obtained. A chest film at this time revealed considerable clearing of the pulmonary infiltrations. A defibrinated blood smear made on the 21st day of therapy revealed only an occasional questionable L.E. cell, and a repeat smear a few days later was completely negative. On the 67th day of ACTH therapy the patient felt completely well except for a rare stab of pleural pain; his chest film was clear except for vague, minimal, residual mottling at the bases; and all other laboratory tests, including electrophoretic analysis of serum proteins, were within normal limits.

ACTH was gradually discontinued for one week. During this the patient developed a swollen, tender right lower leg believed to be due to a deep thrombophlebitis. He was placed on dicumarol and kept in bed for about 6 weeks until the tenderness and swelling in the leg subsided enough to permit ambulation.

Results.—A full 2 months after ACTH was stopped, his status was re-evaluated. He stated that he felt well. He had no chest pain or shortness of breath. Physical examination was negative if he wore an elastic stocking when ambulant to prevent swelling of his right ankle. A chest film (Fig. 4) showed only slight accentuation of the bronchovascular markings in the first and second interspaces on the right and possibly in the bases. Urine analysis, blood count and serum protein determination were within normal limits. Another L.E. cell test was negative. The only abnormality discovered was a persistently elevated sedimentation rate (40, 39, and 33 mm./hr on three determinations.)

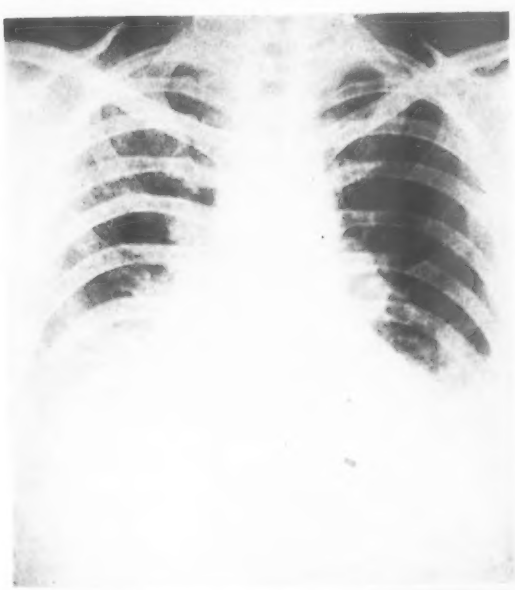
He was therefore discharged to the care of another clinic.

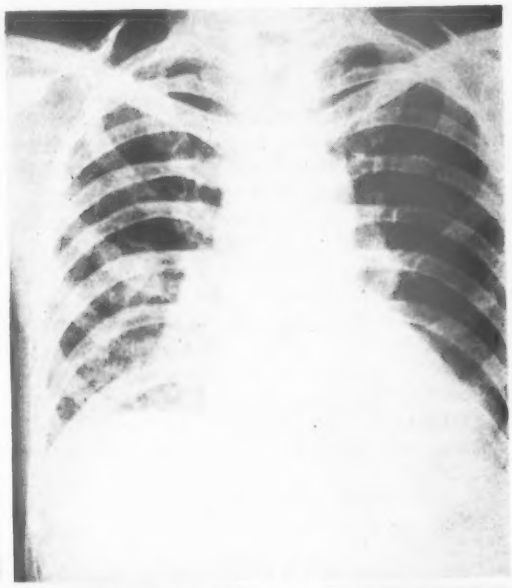
Comment.—This case clearly illustrates that for many months disseminated lupus erythematosus may manifest itself primarily as pulmonary disease. From the onset and throughout the long course of the illness, a bilateral, shifting pneumonitis with pleuritis was the outstanding clinical finding, and drew attention from the signs of other organ involvement. The result was a thorough search for primary pulmonary disease. During the first hospitalization, many sputum cultures for bacteria and fungi, sputum examinations for malignant cells and for eosinophils, tests for cold agglutinins, and a coccidioidin skin test were done. Primary atypical pneumonia, Q fever, psittacosis, and other viral pneumonitides were thought of because of the low white count and the failure to respond to antibiotic therapy. During the second hospitalization studies were repeated to exclude tuberculosis, and the illness was finally considered to be primary atypical pneumonia. In our hospital the diagnoses of sarcoid and of lymphomatous pulmonary infiltrations were at first seriously considered.

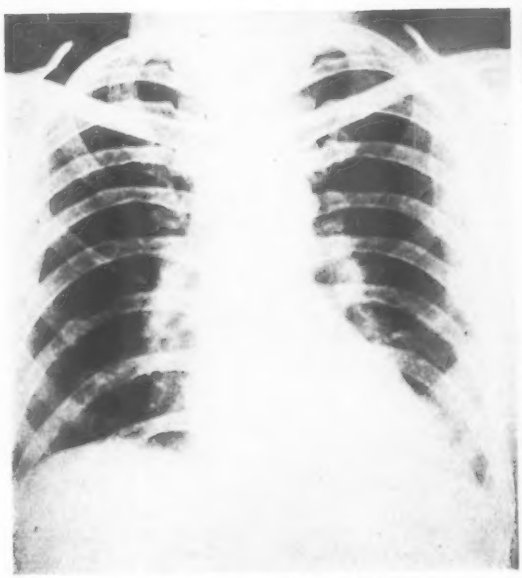
In retrospect, certain clues stand out which point to the correct diagnosis:

(*i*) numbness and tingling of hands and feet;
(*ii*) electrocardiographic evidence of acute pericarditis found during the first hospitalization, and the cardiac enlargement visible on the chest films;
(*iii*) red cells in one urine specimen during the second hospitalization;
(*iv*) borderline elevation of serum globulin discovered during the third hospitalization.

The diagnosis of disseminated lupus erythematosus was suspected late in the course of the first hospitalization but was apparently discarded when L.E. cells were not found in a bone-marrow preparation. We can only speculate as to why the cells were not seen, since later they were easily demonstrated. The patient had been on ACTH therapy for 12 days before the first test was done, but this seems insufficient treatment to have suppressed the phenomenon completely. A better reason is the lack of sensitivity of the bone-marrow technique. Although the details of the procedure used in this instance are unknown, most bone-marrow preparations are made from heparinized marrow after 20 to 30 min. incubation.







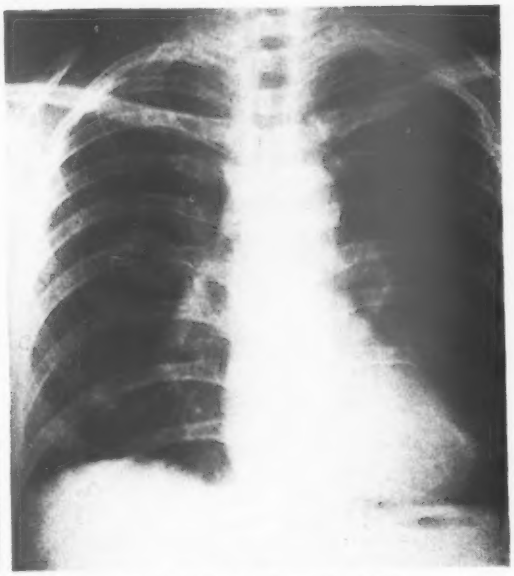


Fig. 1.—Case 1, May 3, 1952.
Fig. 3.—Case 1, August 18, 1952.

Fig. 2.—Case 1, June 19, 1952.
Fig. 4.—Case 1, March 30, 1953.

Zimmer and Hargraves (1952) have shown that a peripheral blood method which permits coagulation to occur, and which provides for a 2-hr incubation period is much more sensitive than the older bone-marrow method. The defibrinated blood technique, which we used to find the L.E. cells, meets these requirements and is one of the most sensitive techniques now available.

The experiences with the L.E. cells tests in this case illustrate two points:

(*i*) when a laboratory test is considered pathognomonic of a disease, a false negative result will usually cause that diagnosis to be discarded despite good evidence in its favour.

(*ii*) when we saw the patient a diagnosis of disseminated lupus could not have been made without a positive L.E. cell test. He had no significant skin lesions, his arthritis was minimal, his pericarditis had subsided, and his urinary sediment was not typical of the disease. The basis for his fever, pulmonary infiltrations, and abnormal serum protein electrophoretic pattern would have remained obscure without the demonstration of the L.E. cells. Perhaps L.E. cells should be searched for more often in patients with similar atypical, persistent pulmonary infiltrations.

The pulmonary lesions in this patient were clinically characterized initially by cough productive of some

mucoid sputum, dyspnoea, and pleural pain. The sputum was never profuse nor purulent. The cough soon became non-productive and disappeared, but the pleurisy and dyspnoea persisted. When the patient was first seen by us, 7 months after the onset of symptoms, the cough was gone, and the severe dyspnoea seemed out of proportion to the findings, though it could be explained in part by the pleural pain. The persistence of pleuritis and the absence of purulent sputum at any time probably reflect an interstitial and largely sub-pleural location of the pneumonitis, and aid in its differentiation from a secondary infective bronchopneumonia.

Figs 1-4 illustrate many of the characteristics described by Thorell (1952), particularly the association of a pleural reaction with mottled and streaky consolidations most prominent in the bases. The shifting nature of the infiltrations is best seen by a comparison of Figs 2 and 3; a large patch of pneumonitis in the right mid-lung field disappeared, but increased density appeared in the left base. Fig. 4, taken 2 months after ACTH therapy was stopped, reveals the clearing which followed prolonged adrenocortical hormone therapy. Subjective improvement, fall of temperature and sedimentation rate to within normal limits, and even disappearance of the L.E. cell phenomenon, preceded maximum clearing of the pulmonary infiltrations radiologically. This shows that ACTH therapy should be prolonged well after the usual signs of disease activity have subsided.

Case 2, a 35-year-old coloured janitor, was admitted to the hospital in October, 1952, because of painful swelling of the fingers, wrists, and toes of 3 wks' duration.

History.—For 2 mths he had noticed increasing weakness, and during this period had lost about 20 lb. He had also received some pills thought to be sulpha-drug tablets and some injections for "infected urine". For 2 yrs he had experienced intermittent anorexia. A systemic review was negative except for a long history of hay-fever. There were no other respiratory symptoms.

Examination.—The patient was thin, and appeared chronically ill, but was afebrile. Head negative. Small, rubbery, non-tender lymph nodes in both posterior triangles of neck.

Cardiovascular system normal except for a questionable Grade 1 apical systolic murmur.

Respiratory rate and excursion normal. Percussion note resonant throughout, but medium, persistent crepitant rales heard over both lower lung fields.

Abdominal and neurological examinations negative.

Enlarged, firm, non-tender lymph nodes also felt in axillae, and in epitrochlear and inguinal areas.

Prominent superficial varicosities of right leg.

Increased warmth and symmetrical fusiform swelling of proximal interphalangeal joints of both hands, wrists, and metatarsophalangeal joints.

Laboratory Data:

Haemoglobin, 15·2 g.; white blood cell counts, 3,300 to 5,800; initial differential count, 41 per cent. neutrophils, 58 per cent. lymphocytes, and 1 per cent. eosinophils. Later differential counts within normal limits.

Sedimentation Rate: 42, 20, and 42 mm./hr (Wintrobe uncorrected).

Urine analyses: specific gravity 1·016-1·024; albumin negative; sugar negative; sediment, few to large numbers of white blood cells, no red blood cells or casts. 24-hour urine protein excretion: 300 mg.

Cardiolipin and Kahn tests: negative. Antistreptolysin titre: 100 Todd units. Differential sheep red cell agglutination test for rheumatoid arthritis: negative.

Blood chemistry: blood urea nitrogen 16 mg. per cent.; cephalin-cholesterol flocculation 1+; thymol turbidity test 3 units; total protein 7·6 g. per cent.; albumin 4·3 g. per cent.; globulin 3·3 g. per cent.

Radiology.—Admission chest film (Fig. 5) disclosed streaky and mottled infiltrations throughout both lower lung fields which were interpreted as bilateral pneumonitis.

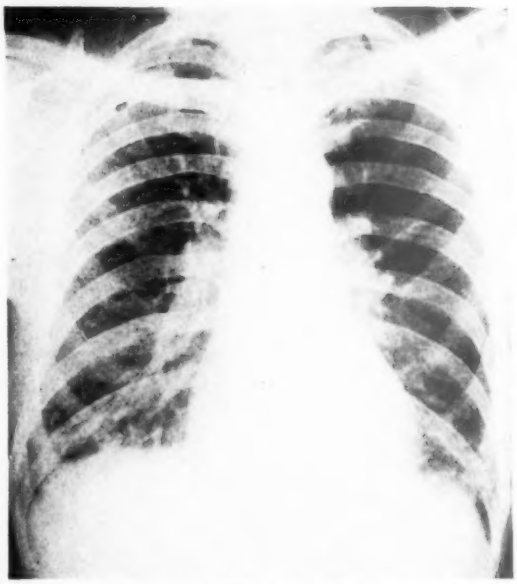


Fig. 5.—Case 2, October 8, 1952, several films taken up to May 9, 1953, are identical.

Skin.—Tuberculin skin test positive. Coccidioidin, histoplasmin, and Frei skin tests negative.

Cultures of three gastric washings grew no tubercle bacilli.

Electrocardiogram.—T wave inversions in leads III and AVF suggestive of posterior wall ischaemia.

Biopsy.—Cervical lymph node revealed only lymphoid hyperplasia; random muscle biopsy was negative.

L.E. Cell Preparation made from heparinized blood after 30 min. incubation showed suspicious rosettes but no definite L.E. cells. Later test, using defibrinated blood incubated for 2 hrs, revealed many typical L.E. cells.

Progress.—At first the patient had intermittent fever to about 100-101° F. The painful swelling of hands, wrists, and feet did not improve, and he developed migratory pain, tenderness, and stiffness of the shoulders, elbows, and knees. Despite the physical and röentgen findings of pulmonary involvement, no cough, sputum, dyspnoea or chest pain was ever noted.

Diagnosis.—When the first L.E. cell test, lymph node biopsy, and muscle biopsy were all reported as negative, a diagnosis of atypical rheumatoid arthritis with rheumatoid lung disease was seriously considered.

Therapy.—About one month after admission ACTH therapy was started. For 4 days 10 i.u. daily were given in 1,000 ml. 5 per cent. dextrose in water, by intravenous drip over an 18-hour period. The dosage was then reduced to 5 i.u. daily.

Results.—Within 24 hours there was definite improvement in his joints. He became afebrile and noted a return of appetite and strength. Only minimal swelling of the fingers could be found after 4 days of treatment, and after 10 days, the palpable lymph nodes were much smaller. However, crepitant rales persisted at both lung bases, and a progress chest film showed no improvement. Because of this, and the establishment of the diagnosis of disseminated lupus erythematosus by the discovery of the L.E. cells on the second preparation, the dosage of ACTH was increased to 10 i.u. daily, maintaining the 18-hour duration. This was continued for 2 weeks until a pronounced Cushing effect with mild diastolic hypertension was obtained, and it was felt that the dosage could be lowered to 5 i.u. again. ACTH therapy was continued for a total of almost 10 weeks, with maintenance of the Cushing effect throughout the remainder of this period. The patient felt completely well and was impatient to leave the hospital, but there was no improvement in his pulmonary findings, and his sedimentation rate was not always within the normal range, and the T wave inversions in leads III and AVF persisted. Despite these findings, ACTH therapy was discontinued to determine whether or not cortisone maintenance therapy would be required to prevent progressive and disabling disease activity. He was given leave for a short period on no therapy. When recalled, 7 weeks after the end of treatment, he stated that he felt well. There was no evidence of joint disease. Slight lymphadenopathy was found. Rales were still heard at the lung bases, and a chest film was identical with the first film taken 6 months earlier. A white blood cell count was 4,000 with a normal differential. Urine analysis was normal.

He was permitted to return to his work as a janitor, but within a few weeks a relapse became gradually apparent, and he was therefore re-admitted. He again responded promptly to ACTH therapy, but *x*-ray examination showed that the pulmonary infiltrates remained unaltered. It is now thought that continuous maintenance therapy will be required, particularly if the patient is to find employment.

Follow-up.—This patient was seen on November 12, 1953; he seemed well and had no complaints, but râles were still present at both bases posteriorly. He had had no therapy for 2 months. It was evident that the remission was precarious and incomplete.

Comment.—On purely clinical grounds, it was impossible to distinguish the manifestations of disseminated lupus erythematosus (without lupus) in this Negro from either polyarthritis attributable to sarcoidosis, of which ten cases are described in the world literature (Myers and others, 1952), or from rheumatoid arthritis with pulmonary lesions, of which but five published cases have been directly reported (Ellman and Ball, 1948; Bloom and Rubin, 1950; Leys and Swift, 1949). One difference from sarcoidosis appeared in retrospect, *i.e.* the absence of hilar lymphadenopathy in our patient as contrasted with its presence in each of the four cases of sarcoidosis with polyarthritis reported by Myers and others. However, that diagnosis was excluded by the negative lymph node and muscle biopsies.

The joint manifestations of lupus erythematosus and rheumatoid arthritis may be indistinguishable, even to the *x*-ray finding of a destructive joint process in the former (Tumulty and Harvey, 1949). As in this patient, the haemagglutination test for rheumatoid arthritis as modified by Heller and others (1949) may not be applicable in the absence of *x*-ray evidence of joint damage. Synovial punch biopsy would seem of limited value in the differentiation of the two conditions. Therefore, when polyarthritis suggestive of rheumatoid arthritis is associated with pulmonary lesions, it would seem important to look carefully for L.E. cells. They may furnish, as in this instance, the only direct approach to the correct diagnosis.

The complete absence of respiratory symptoms over many months despite the extensive, unchanging infiltrations seen on the chest films is further evidence of an interstitial location of the pulmonary lesion. The failure to find significant pleural involvement over many months indicates that the combination of a parenchymal and pleural lesion is not a prerequisite to the diagnosis of pulmonary lupus erythematosus. However, it is likely that evidence of pleuritis will be found at some time in most cases. Unlike Case 1, the pulmonary lesions in Case 2 remained unchanged during a course of ACTH therapy which was adequate to produce striking clinical remission of more symptomatic facets of the disease as well as Cushing's syndrome.

Summary

The published descriptions of pulmonary parenchymal lesions in disseminated lupus erythematosus are reviewed, and two cases are reported which illustrate the clinical manifestations of such lung lesions. An awareness of their frequency and atypical behaviour is necessary for two reasons:

(*i*) to recognize cases in which pulmonary infiltrates are the major symptom of disease,

(*ii*) to differentiate, in established cases, primary parenchymal disease from a secondary infective pneumonia.

In the first patient here reported, a bilateral, shifting pneumonitis with pleuritis so overshadowed evidence of other organic involvement that an extensive search was made for primary pulmonary disease. In the second patient, the combination of bilateral pulmonary infiltrates, peripheral lymphadenopathy, and polyarthritis closely mimicked sarcoidosis with polyarthritis, and rheumatoid lung disease. A correct diagnosis was established only after the demonstration of typical L.E. cells.

Dyspnoea and pleural pain were the respiratory complaints of one patient. The other patient was asymptomatic. The absence of cough and purulent sputum is evidence of an interstitial location of the pulmonary lesion.

The *x*-ray findings in the first case consisted of

shifting, patchy, mottled densities, most pronounced in the bases, and associated with a pleural reaction. In the second case, there were extensive, streaky, mottled infiltrates throughout both lower lung fields without evidence of pleuritis.

The response of the pulmonary lesions to ACTH therapy varied; in one patient there was complete clearing, and in the other the pulmonary lesions remained unchanged, despite ACTH therapy sufficient to induce a pronounced Cushing effect.

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Lésions pulmonaires du lupus érythémateux disséminé

RÉSUMÉ

On passe en revue les descriptions publiées des lésions pulmonaires parenchymateuses dans le lupus érythémateux disséminé et on relate à titre d'exemple deux cas de telles manifestations pulmonaires cliniques. La connaissance de leur fréquence et de leur comportement atypique est nécessaire pour deux raisons:

(*i*) pour reconnaître les cas dans lesquels les infiltrats pulmonaires constituent le symptôme majeur de la maladie;

(*ii*) pour différencier, à la période d'état, entre la maladie parenchymateuse primaire et la pneumonie infectieuse secondaire.

Dans le premier cas une pneumonite bilatérale migratrice avec pleurite éclipsait les signes de l'atteinte des autres organes à un tel point qu'on a fait des recherches approfondies pour trouver la maladie pulmonaire primaire. Dans le deuxième l'ensemble des infiltrats pulmonaires bilatéraux, de la lymphadénopathie périphérique, et de la polyarthrite simulait une sarcoïdose accompagnée d'une polyarthrite et de la maladie pulmonaire rhumatismale. On ne fit le diagnostic correct qu'après avoir trouvé les cellules typiques du lupus érythémateux.

Du coté respiratoire, l'un des malades se plaignait de dyspnée et de douleur pleurale, l'autre ne présentait aucun symptôme. L'absence de la toux et de l'expectoration purulente indique qu'il s'agissait d'une localisation intersticielle de la lésion pulmonaire.

Radiologiquement, il y avait chez le premier malade des condensations mobiles, inégales et tachetées, plus prononcées aux bases et associées à une réaction pleurale. Chez le deuxième il y avait des infiltrats étendus, striés et tachetés aux deux bases pulmonaires sans signes de pleurite.

La réponse des lésions pulmonaires au traitement par l'ACTH était variable. Chez un malade on a observé la guérison complète; chez l'autre les lésions pulmonaires ont demeuré, malgré le traitement par l'ACTH suffisant à provoquer un effet de Cushing prononcé.

Lesiones pulmonares del lupus eritematoso diseminado

SUMARIO

Se revisan las descripciones publicadas de las lesiones pulmonares parenquimatosas en el lupus eritematoso diseminado y se relatan dos casos ilustrativos de tales manifestaciones pulmonares en clínica. El conocimiento de su frecuencia y de su comportamiento atípico es necesario por dos razones:

(*i*) para reconocer los casos en que los infiltrados pulmonares constituyen el síntoma mayor de la enfermedad;

(*ii*) para diferenciar, en casos establecidos, entre la enfermedad parenquimatosa primaria y la neumonia infecciosa secundaria.

En el primer caso una neumonitis bilateral móvil con pleuritis eclipsó las manifestaciones en otros órganos de manera que se hicieron investigaciones extensas en busca de la enfermedad pulmonar primaria. En el segundo el conjunto de infiltrados pulmonares bilaterales, de linfadenopatia periférica y de poliartritis hizo pensar a una sarcoidosis con poliartritis y con enfermedad reumatoide del pulmón. Tan sólo el hallazgo de las células típicas del lupus eritematoso llevó al diagnóstico correcto.

Del lado respiratorio, un enfermo se quejó de dispnea y de dolor pleural, el otro no tuvo síntoma alguno. La ausencia de la tos y de la expectoración purulente indica una localización intersticial de la lesión pulmonar.

Radiológicamente, en el primer enfermo hubo sombras móviles, moteadas y abigarradas, más pronunciadas en las bases y asociadas con una reacción pleural. En el segundo hubo infiltrados extensos, rayados y moteados en la parte inferior de ambos pulmones sin manifestaciones de pleuritis.

La respuesta de las lesiones pulmonares al tratamiento con ACTH fué variable. El primer enfermo curó completamente; en el segundo las lesiones pulmonares permanecieron a pesar del tratamiento con ACTH, suficiente para producir un efecto pronunciado de Cushing.

PRODUCTION OF ARTHRITIS IN THYROPARATHYROIDECTOMIZED RAT BY INJECTIONS OF DEOXYCORTONE ACETATE

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Selye and others (1944) claimed that certain "diseases of adaptation", including arthritis, nephrosclerosis, and periarteritis nodosa, could be produced in rats which are subjected to unilateral nephrectomy, injected with deoxycortone acetate (DCA) and given 1 per cent. saline to drink. Harrison (1946) was at first unable to produce arthritis in rats by these methods, and later (Harrison, 1951a) showed that the manner of removing the left kidney in the experiments is an important factor. If, during the operative removal of the left kidney, the inferior adrenal arteries arising from the renal artery are deliberately or inadvertently interrupted, an area of focal necrosis in the zona fasciculata of the ipsilateral adrenal cortex results (Harrison, 1951b). Experimental arthritis could only be produced by injections of DCA in rats possessing such a focal necrosis of the adrenal cortex. This experimental observation is interesting from the clinical viewpoint, since focal necrosis in the z. fasciculata of the rat adrenal cortex might be expected to cause a primary reduction in the secretion of gluco-corticoids (including cortisone), and a dissociation of the normal relationships of gluco-corticoid and mineralocorticoid secretion, which would be enhanced by the DCA injections. This adrenal cortical relationship appears to be peculiar to arthritis only, and not to the other diseases of adaptation investigated (Harrison, 1952).

If this theory is correct, it should be possible to produce arthritis by injections of DCA in rats in which an atrophy of the z. fasciculata of the adrenal cortex has been effected by other means. It was therefore decided to determine whether injections of DCA would induce arthritic changes in the thyroparathyroidectomized rat, since after this latter procedure not only is there an overall decrease in weight and size of the adrenals due to a fall in basal metabolic rate, but also the z. fasciculata atrophies markedly (Deane and Greep, 1947).

Material and Methods

In this experiment 24 immature female albino rats, varying in weight from 31 to 63 g. were used. Littermates were divided equally into two groups. The mean body weight of rats in Group I was 41·5 g., in Group II 43·9 g. Animals of both groups were subjected to thyroparathyroidectomy, while the left kidney in rats of Group II was simultaneously removed in addition, taking care not to damage the adrenal blood vessels or to handle the kidney unduly lest vasoconstriction should occur in the renal artery and possibly the inferior adrenal arteries. Removal of the thyroid in the rat necessitates removal of the parathyroids which are embedded in it; the small size of the thyroid and the microscopic size of the parathyroids effectively precludes any attempt at separating the latter and grafting them into the wound post-operatively. In addition to being given 1 per cent. saline to drink instead of tap-water throughout the experiment, all rats were therefore provided with powdered calcium lactate *ad lib.* on a tray throughout the post-operative period. All rats of both groups were fed on a diet similar in composition to "purina fox chow", and were kept in a thermostatically controlled animal house free from draughts at a temperature of 71° to 85° F. (Fig. 1). Commencing on the fifth day after operation, all rats of both groups were injected subcutaneously twice daily with 2 mg. DCA from an aqueous suspension containing 20 mg. DCA per ml. and 0·1 per cent. cetrimide

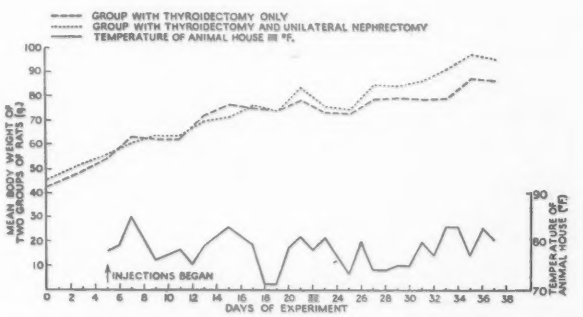

Fig. 1.—Mean body-weight gain in two groups of rats throughout experiment, and animal-house temperature.

(Harrison, 1951a). Injections were continued until the 37th day after operation, when all surviving rats were killed.

The experimental technique therefore provided two groups of rats given 1 per cent. saline to drink, injected with DCA, and fed on "purina fox chow" and calcium lactate: Group I, thyroparathyroidectomized, and Group II, thyroparathyroidectomized and unilaterally nephrectomized. By such methods it was hoped to determine whether arthritis could be produced by ablation of the thyroid, if atrophy of the z. fasciculata of the adrenal cortex is essential for the production of experimental arthritis, and whether removal of the left kidney without involving the adrenal blood supply is essential for, or helpful in, the production of arthritis.

The adrenals, kidneys, heart, hind feet, and lungs were removed at autopsy from all rats, fixed immediately, cut, and stained. The adrenals were fixed in formal calcium and treated with Sudan black for the detection of lipoids, or the acid haematein test (Baker, 1946) for phospholipids. The other tissues were fixed in Zenker-formol, and the joints embedded in low-viscosity nitrocellulose before sectioning.

Results

Two animals of Group I and three of Group II died during the night within the first 7 days after operation. Six other rats of Group II either died, or became moribund and were killed, on the 16th, 19th, 21st (two rats), 25th, and 30th days after operation, from pneumonitis or pneumonia. Ten Group I rats, and only three Group II rats survived until the end of the experiment (37th day after operation). The mean growth rate curves of the two groups of animals throughout the experiment are virtually identical (Fig. 1), and therefore the two groups are strictly comparable in the efficiency of the thyroidectomy, food intake, and other factors influencing body weight. The mean growth curves of the rats in each cage are also parallel. As shown in Fig. 1 there is also a suggestion of some correlation between body weight and animal house temperature. No thyroid tissue was found in any of the rats at autopsy.

Joints.—Frank arthritis, an unquestionable swelling of the joint together with redness of the overlying skin, was noticeable to the naked eye in the hind feet of eight rats during the course of the experiment. The arthritis was noticed first in a thyroparathyroidectomized and unilaterally nephrectomized rat of Group II on the 15th day of the experiment. Three more Group II rats developed arthritis in the ankle or tarsal joints (Figs 2 and 3) on the 17th day, and one other rat of this group on the 19th day. The arthritic joints were warm to touch, and tender. The arthritic appearance lasted for some 3 days in all cases and then regressed. Such an obvious arthritis

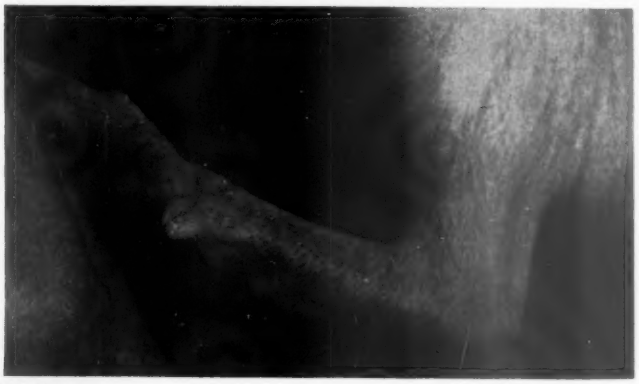

Fig. 2.—Hind foot of rat showing arthritis in tarsal region.

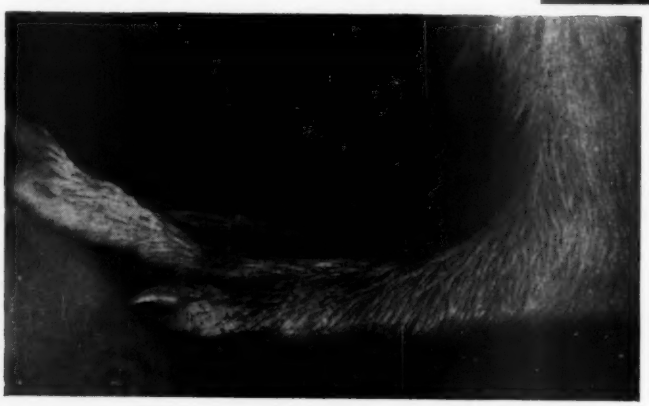

Fig. 3.—Hind foot of non-arthritic rat for comparison with Fig. 2.

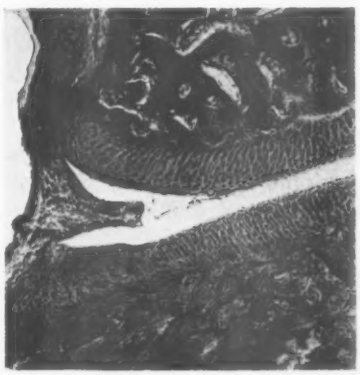

Fig. 4.—Ankle joint of rat of Group II which died on 21st day of experiment, showing slightly oedematous synovial villus with some degree of cellular infiltration. (× 24.)

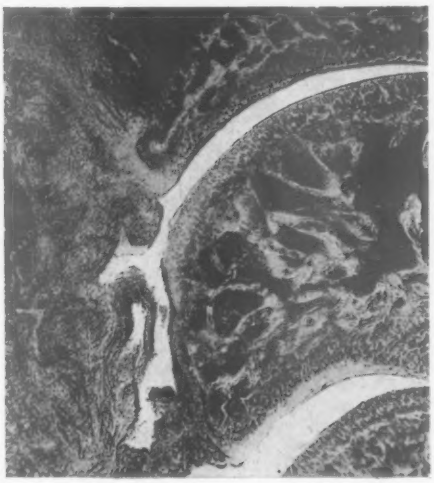

Fig. 5.—Ankle joint of Group II rat which became moribund and was killed on 21st day of experiment, showing marked oedema of synovial tissues. (× 24.)

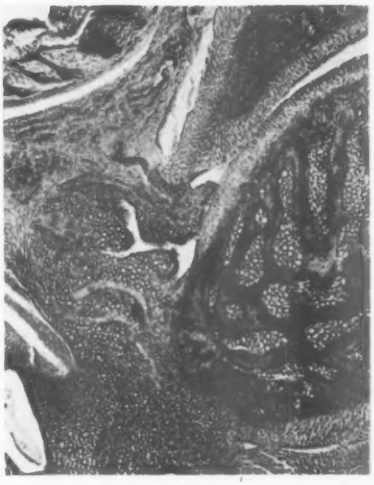

Fig. 6.—Ankle joint of Group I rat, showing proliferation and enlargement of synovial villi at termination of experiment. (× 24.)

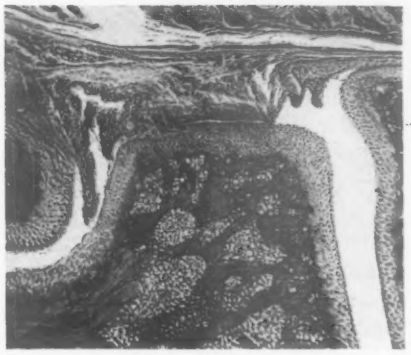

Fig. 7.—Coronal section through ankle joint of Group I rat, showing proliferation of synovial villi at end of experiment. (× 24.)

did not appear in rats of Group I until the 31st-33rd days of the experiment, when three rats displayed frank arthritis in one or both hind feet exactly similar to that which occurred in the Group II rats. On the 17th-19th days of the experiment five rats of Group I and three of Group II showed appearances in their hind feet very suggestive of arthritis, with redness, tenderness, and very slight swelling of the ankle joint. At no time did arthritis develop in the fore feet of any rat.

Microscopically the joints of the hind feet of all rats of both groups killed from the 19th day of the experiment onwards were very similar in appearance to the human rheumatoid type of arthritis. All grades of synovial involvement could be found, from slight proliferation and hyperaemia on the 21st day (Figs 4 and 5) to definite enlargement, proliferation, and cellular infiltration of the synovial villi (Figs 6 and 7) in all rats of both groups killed at the end of the experiment. The histological signs of arthritis in the joints of the two groups did not differ in the same way as the time of onset of macroscopic lesions. In general, the later in the experiment the rat was killed, the more severe the joint involvement.

As early as the 21st day after operation, cartilage cells in the superficial layers of articular cartilage showed marked degeneration (Fig. 8), and the cells in the articular cartilage of all arthritic joints contained prominent pleomorphic basophilic bodies (Fig. 9, overleaf), which might become extracellular towards the superficial surface of the

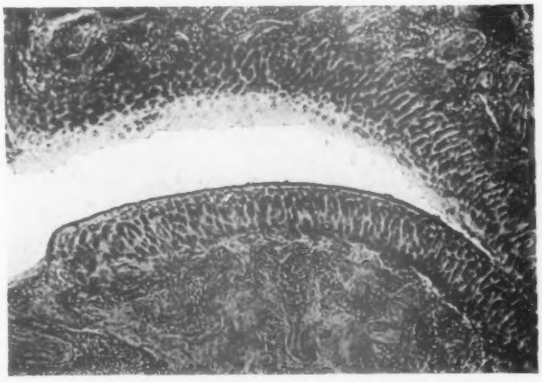

Fig. 8.—Degeneration of cartilage cells in superficial layers of articular cartilage at lower end of tibia (top) in rat killed on 21st day of experiment. Normal articular cartilage covering upper surface of talus can be seen in lower part of figure. (× 53.)

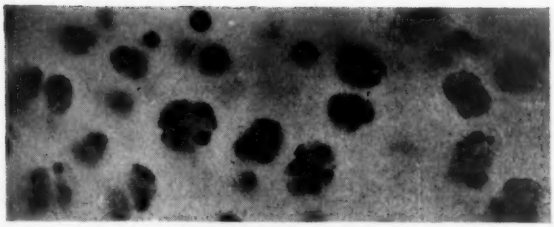

Fig. 9.—Intracellular basophilic bodies in cells of articular cartilage at lower end of tibia of Group I rat killed at end of experiment. (× 460.)

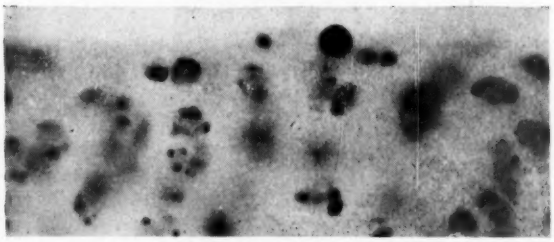

Fig. 10.—Surface of articular cartilage at lower end of tibia of Group I rat killed at end of experiment. A "pyknotic sphere" may be seen being extruded from surface of cartilage in upper part of figure. Cartilage cells contain basophilic bodies. (× 460.)

cartilage. Such bodies are difficult of explanation; they are too large to be virus inclusion bodies, and too pleomorphic to be bacteria, even the pleuropneumonia group of organisms. These bodies may occasionally be found in the joint space, sometimes with larger pyknotic spheres (Fig. 10), very similar to the structures found in the seminiferous tubules of the rat testis following ischaemia (Oettlé and Harrison, 1952). The joint cavity was never found to contain leucocytes as in previous experiments (Harrison, 1951a), bacteria, or large accumulations of joint fluid. In many joints the synovial membrane encroached on to the surface of the periphery of the articular cartilage (Fig. 11); in other joints definite premonitory signs of erosion were noticed; in one ankle joint a definite erosion occurred (Fig. 12). Changes suggestive of derangement of the epiphyseal cartilage, and even decalcification and slight absorption of some phalangeal elements, could be seen. In one rat a granuloma involving the periosteum of a metatarsal (Fig. 13) was a notable feature.

Adrenals.—Unlike previous experiments (Harrison, 1951a), neither the gross histological nor the histochemical appearances of the adrenal cortex gave any assessment of the state of its secretory activity in relation to the arthritic process. This is due to two features. First, since the animals which died or were killed during the course of the experiment had a lung infection, the adrenal cortices of such rats were invariably hypertrophied, and can only be considered as reflecting the response to infection; secondly, the interval between the occurrence of macroscopic signs of arthritis and the termination of the experiment varied in different rats in the two groups. Thus, the adrenal of a rat dying on the seventh day of the experiment (Fig. 14), although large, is not as markedly hypertrophied, nor as sudanophilic, as that of a rat killed on the 21st day of the experiment (Fig. 15) immediately after the occurrence of arthritis on 2 successive days. There is little difference

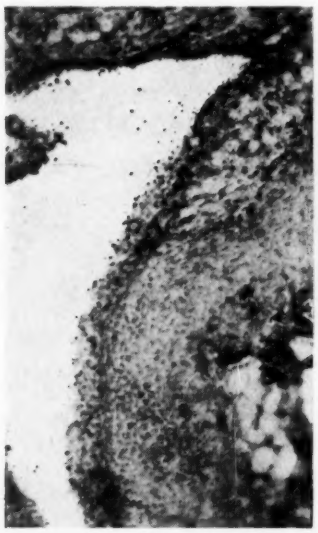

Fig. 11.—Synovial membrane encroaching on to surface at periphery of articular cartilage at lower end of tibia in Group II rat killed at end of experiment. (× 83.)

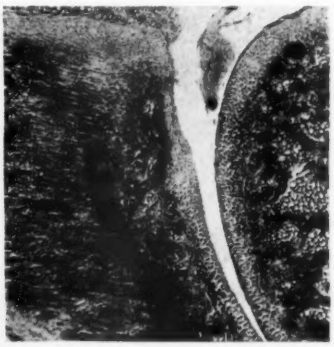

Fig. 12.—Erosion of articular cartilage at lower end of tibia in Group II rat killed at end of experiment. Erosion may be seen at top of figure. (× 24.)

Fig. 13.—Granuloma involving periosteum of metatarsal of Group II rat killed at end of experiment. (× 24.)

Fig. 14.—Adrenal cortex of Group II rat which died on 7th day of experiment. Sudan black coloration not very dense. (× 9.)

Fig. 15.—Adrenal cortex of Group II rat which died on 21st day of experiment after occurrence of arthritis on two successive days. Sudan black more marked at periphery of z. fasciculata, and adrenal larger than in Fig. 14. (× 9.)

Fig. 16.—Adrenal cortex of Group II rat killed at end of experiment, which had macroscopic arthritis on 17th day. Sudanophilia more marked than in Figs 14 and 15. (× 9.)

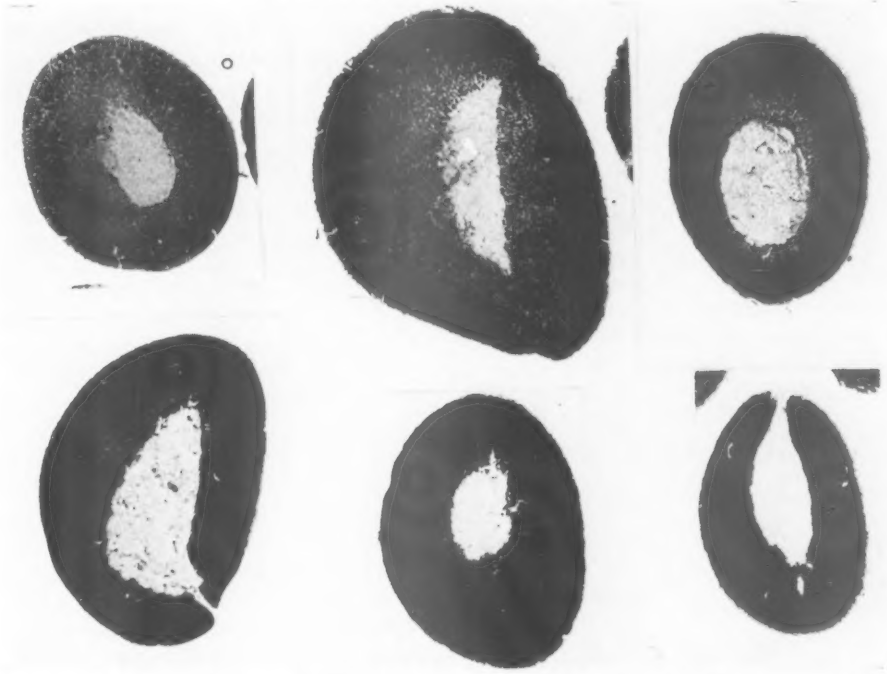

Fig. 17.—Adrenal cortex of Group II rat, killed at end of experiment, which had no macroscopic evidence of arthritis. Adrenal is slightly larger and more markedly sudanophilic than that in Fig. 16. Sudan black. (× 9.)

Fig. 18.—Adrenal cortex of Group I rat, killed at end of experiment, which had no macroscopic evidence of arthritis. Adrenal is about the same size as that in Fig. 16, but cortex more uniformly sudanophilic. Sudan black. (× 9.)

Fig. 19.—Adrenal of Group I rat, killed at end of experiment, which had no macroscopic evidence of arthritis. Although this rat was similar to that in Fig. 18, the adrenal is smaller, and its zona reticularis less well marked. Sudan black. (× 9.)

between the adrenal cortices of two rats of Group II which survived to the end of the experiment: one (Fig. 16) had macroscopic signs of arthritis on the 17th day of the experiment, and the other (Fig. 17) had no such signs, but both, of course, showed microscopic arthritis at the end of the experiment; but it may be noticed that the adrenal in the latter is slightly larger and its cortex more markedly sudanophilic. Nor is there any marked difference between the adrenal cortices of these two rats, and that of one (Fig. 18) of Group I which had no macroscopic arthritis throughout the experiment, though histological signs of arthritis were found at autopsy. Yet the adrenals of another rat of Group I similar in body weight and experimental behaviour to the latter, were much smaller and had a less marked z. reticularis (Fig. 19). It may be noted, however, that the adrenal cortex in all rats killed at the end of the experiment was more markedly sudanophilic than in the two rats killed on the 7th and 21st days of the experiment.

The distribution of phospholipid in adrenals of the two groups (Figs 20 and 21, overleaf) is also virtually identical and independent of the presence of arthritis. Although there was no histological appearance of the adrenal cortex in these experiments which could be identified with the occurrence of arthritis, it must be stressed that the histology of the adrenal cortex at the time of onset of the arthritis will obviously give a true picture of its status at that time, and there was no opportunity of such an examination in this experiment in a rat free from the complication of lung infection. Even experimental focal necrosis of the adrenal cortex, which may be a factor in the aetiology of arthritis in rats, can be detected only in its early stages (Harrison, 1951a). Nevertheless, there was a suggestion of diminution in width of the adrenal cortex of many rats in this experimental series, as has been described in thyroparathyroidectomized rats by Deane and Greep (1947). The z. glomerulosa in all rats of both groups showed diminution in lipoid and phospholipid content which

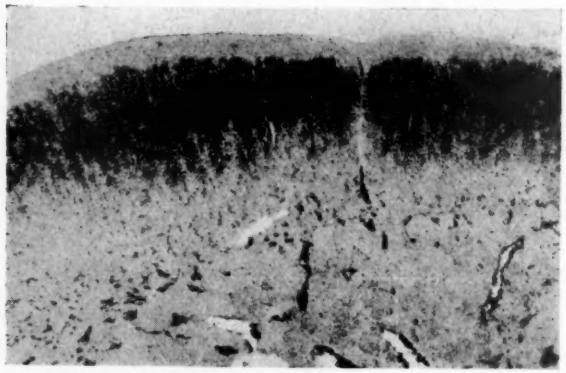

Fig. 20.—Distribution of phospholipid in adrenal cortex of Group I rat. Note absence of coloration in zona glomerulosa. Phospholipid confined to outer zona fasciculata. (× 40.)

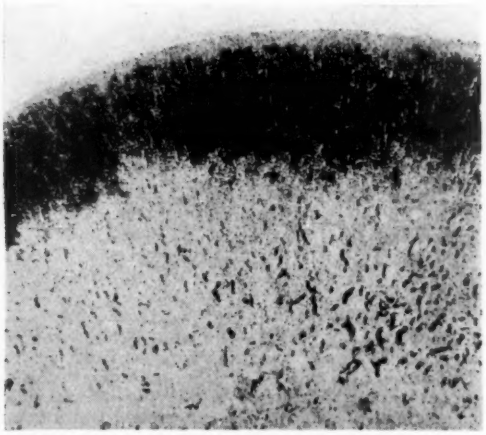

Fig. 21.—Phospholipid in adrenal cortex of Group II rat similar in experimental behaviour to that in Fig. 20. Distribution of phospholipid almost identical. Wider adrenal cortex accounted for by differences in body weight of animals at autopsy. (× 40.)

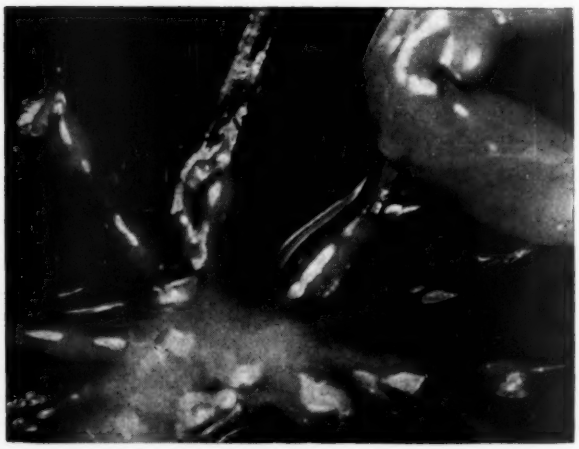

Fig. 22.—Nodules of periarteritis in mesentery of Group II rat killed at end of experiment.

was due to the DCA treatment, but several rats did not show complete depletion of this zone, possibly because thyroparathyroidectomy itself causes increased lipoid content in this zone (Deane and Greep, 1947). There was no focal necrosis in the adrenal cortices of any of the rats used in this experiment, which confirms the avoidance of damage to inferior adrenal arteries during the nephrectomy at operation in Group II rats.

Heart, Kidneys, and Mesentery.—The histological appearances of the hearts and kidneys of all rats are within normal limits, and no pathological processes such as nephrosclerosis, Aschoff bodies, or Anitschkow myocytes could be found. If the conclusions of Harrison (1952) be accepted, it is therefore improbable that the adrenals in the rats of this experiment are normal. In one Group II rat gross and microscopic signs of periarteritis nodosa were present in the mesentery (Figs 22 and 23).

Discussion

It is not possible to produce arthritis by injections of DCA in rats having normal adrenals (Harrison, 1946, 1951a, 1952). The experiments reported in this communication demonstrate that arthritic changes can be induced in thyroparathyroidectomized rats by these injections. It is quite possible, therefore, that the effect of this operation on the z. fasciculata of the adrenal cortex may have been largely instru-

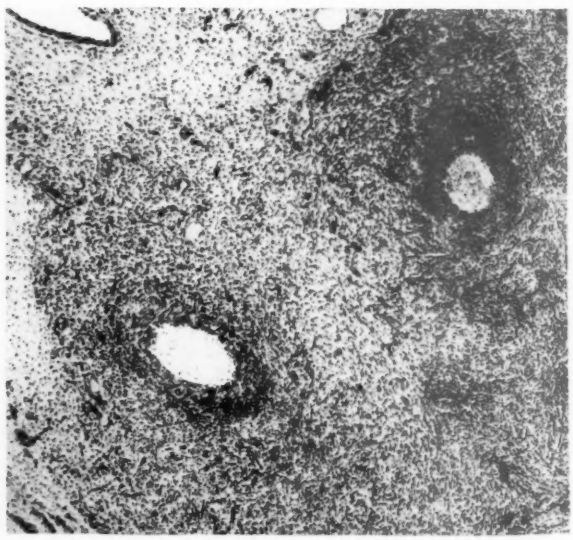

Fig. 23.—Histological appearance of periarteritis nodosa shown in Fig. 22. (× 39.)

mental in the causation of the arthritis. Selye and others (1944) claimed that thyroidectomy greatly facilitated the production of joint lesions in rats injected with DCA, since they were able to obtain arthritis at room temperature in rats which were neither thyroidectomized nor adrenalectomized. In this laboratory arthritis has only been shown to occur in DCA-injected rats after thyroidectomy or adrenal cortical necrosis.

In previous experiments (Harrison, 1951a) it was claimed that unilateral nephrectomy affects the experimental production of arthritis by causing a focal necrosis of the z. fasciculata of the adrenal cortex. It is obvious from the present experimental series that unilateral nephrectomy not involving the adrenal blood supply is not essential for causing arthritis in the thyroparathyroidectomized rat, but there is a suggestion that it does aid the more rapid onset of macroscopic joint lesions. These experiments also demonstrate that, whereas the naked-eye appearance of arthritis is fleeting, the histological lesions in the joints are progressive in character. No leucocytes were found in the joints, as in previous experiments (Harrison, 1952) in which the arthritis was produced by adrenal cortical necrosis.

One striking feature in this investigation was the number of rats in Group II which became moribund with pneumonitis or pneumonia during the course of the experiment. This was not seen in any of the Group I rats, although they were in cages in close proximity to those of Group II. The two groups differ only in the unilateral nephrectomy performed in the Group II rats, and it is possible that this may have been an aetiological factor in the pulmonary lesions, perhaps through the mechanism of fluid imbalance, particularly since many of the Group II rats developed ascites at some point during the experiment. Since unilaterally nephrectomized rats in previous experiments have not shown pulmonary lesions, it appears that the thyroparathyroidectomy is important for their production. This confirms the relatively high incidence of pneumonia in thyroparathyroidectomized and unilaterally nephrectomized rats in the experiments of Selye and others (1944).

The importance of "stress" in experiments such as this has been over-emphasized by many authors. It has become almost customary for freak results or abnormal and unexpected findings to be labelled "probably due to stress caused by . . .". As a result of this scapegoat treatment it is well not to attribute anything to "stress" which has not been carefully considered first. In this experiment the rats were killed by chloroform overdosage, and the adrenals were placed in the fixative within a few minutes. In this matter of killing experimental animals there is lack of unanimity almost to the point of hysteria; a belief that results are incomparable since one author kills rats by chloroform overdosage, and another by decapitation. Yet this is to a large extent invalid, since the adrenals of littermate rats killed simultaneously show the same picture whether chloroform overdosage, decapitation, coal gas, or nembutal overdosage is used (Cain and Harrison, 1950). It is much more important to use littermate animals, a fact often ignored.

All rats of the same group were kept together, six to a cage. The method of placing one rat to a cage was avoided since rats are sociable animals by nature, and separating them may cause as much "stress" as the small amount of fighting which occurs when the rats are together. This can readily be demonstrated by separating a rat from its littermates and then releasing it, when the animal will return to its mates and try to find a way into their cage. Other "stresses" to which the rats were subjected, e.g. subcutaneous injections, were unavoidable and minor in nature.

The experiments reported in this communication may have considerable clinical value. Most investigators report improvement of arthritis by thyroid medication only when frank hypothyroidism is present. Yet Mandl and Gyri (1952) have had considerable cortisone-like success in the treatment of arthritis by the implantation of goitrous thyroid tissue. It may well be advisable to re-investigate the relationship of thyroid hypofunction to human arthritis.

Summary

(1) Injections of DCA in the thyroparathyroidectomized albino rat produce macroscopic evidence of arthritis, which is fleeting. Microscopically the arthritis appears to be progressive in nature.

(2) Unilateral nephrectomy hastens the onset of naked-eye evidence of arthritis, but is not *per se* a prerequisite for the production of joint lesions.

(3) These changes are probably due to a hypofunction of the zona fasciculata of the adrenal cortex consequent on thyroparathyroidectomy.

(4) The clinical relationships and the importance of "stress" in this study are discussed.

This research was aided by a grant from the Medical Research Council. We are indebted to Dr. W. J. Tindall, Organon Laboratories Ltd., for the supplies of DCA used in these experiments, and to Lever's Cattle Foods, Ltd., Bebington, Cheshire, for manufacturing a diet similar in composition to "purina fox chow". We also wish to thank Mr. L. G. Cooper and Miss B. Birkett for their technical assistance.

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Arthrite provoquée par des injections d'acétate de deoxycortone chez des rats thyroparathyroïdectomisés

RÉSUMÉ

(1) Des injections d'acétate de deoxycortone aux rats thyroparathyroïdectomisés déclanchent des signes macroscopiques d'arthrite qui est éphémère. Microscopiquement cette arthrite semble être de nature évolutive.

(2) Une néphrectomie unilatérale accélère le début des signes d'arthrite observables à l'oeil nu, mais elle n'est pas, par elle même, une condition préalable pour produire des lésions articulaires.

(3) Ces altérations sont probablement dues à la hypofonction de la zone fasciculée de l'écorce surrénale à la suite de la thyroparathyroïdectomie.

(4) On discute les implications cliniques de cette étude et l'importance de la "fatigue".

Artritis producida por inyecciones de acetato de deoxicortona en ratas tiroparatiroidectomizadas

SUMARIO

(1) Inyecciones de acetato de deoxicortona en ratas tiroparatiroidectomizadas producen manifestaciones macroscópicas de artritis que es transitoria.

(2) Una nefrectomia unilateral acelera la aparición de los signos de artritis directamente observables pero no es, po si misma, una condición previa para producir lesiones articulares.

(3) Estas alteraciones se deben probablemente a la hipofunción de la zona fasciculata de la corteza suprarrenal como consecuencia de la tiroparatiroidectomia.

(4) Se discute en este estudio las implicaciones clínicas y la importancia de la "fatiga".

FINGER CONTRACTURES DUE TO TENDON LESIONS AS A MODE OF PRESENTATION OF RHEUMATOID ARTHRITIS

BY

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Contractures of the fingers producing a claw hand may be due to nerve lesions (ulnar palsy), muscle lesions (haemophilia or traumatic Volkman's contracture and dermatomyositis), skin lesions (scleroderma), fascial lesions (Dupuytren's contracture), joint lesions (rheumatoid arthritis or osteo-arthritis), or lesions of the tendons and tendon sheaths. The most common lesion of the tendon is a traumatic thickening leading to the snapping finger, usually single, occasionally multiple, and often related to occupation. In gout, uric acid accumulations may occur in the tendon, producing limitation or even "ankylosis" of the fingers without the joints themselves being involved. In rheumatic fever, nodules may form in the tendons of the palm, producing a sticking finger (Scheele, 1885; Keil, 1938; Berkowitz, 1912), but these invariably straighten out again without residue in the course of a few days or weeks (Bywaters, 1951). Similar contractures occur in the palindromic type of rheumatoid arthritis (Bywaters, 1949), and in cases of lupus erythematosus. These reversible contractures need no special therapeutic measures. In rheumatoid arthritis, however, tendon lesions are not only common, occurring in 48 per cent. of cases (Helweg, 1924), 47 per cent. (Edström, 1945), or 42 per cent. (Kellgren and Ball, 1950), but are of the greatest importance from the therapeutic viewpoint. Left untreated, they not only produce such limitation of finger extension that the patient becomes severely handicapped, but, after a time, they may become irreversible through secondary changes in other tissues. It is, therefore, important from the practical aspect to recognize these changes early. While there is little difficulty in their recognition in a frank case of rheumatoid arthritis, it is perhaps rather more difficult to diagnose the tendinous lesions of rheumatoid arthritis in the absence of arthritis. This paper, therefore, describes three cases where the tendon lesions were the presenting sign and joint lesions were either absent or asymptomatic and minimal. A fourth case where joint lesions preceded tendon involvement is included for the discussion of treatment.

The methods used to assess the results of treatment included measurements of gripping strength (Ansell and Bywaters, 1952) and of the palmar contact area. To obtain the latter the palmar aspect of the hand was well inked and then pressed firmly on to paper secured on a flat table. The inked area was then measured with a planimeter.

Case Reports

Case 1.—This girl was admitted in March, 1952, because of inability to straighten her fingers.

In December, 1951, when aged 16, she developed painless swelling of the dorsum of each hand, followed some 10 days later by swelling of the ankles and dorsa of the feet. Shortly afterwards she had aching in the wrists with paraesthesia of the fingers and the swelling of the left hand became much worse. The swelling of the hands and feet gradually subsided without any specific therapy, but as this happened the patient noticed stiffness of the fingers and inability to straighten them; this was 3 weeks before admission and 2 months from onset.

At the age of 6, during an attack of enteritis, a murmur had been noted in the heart, because of which she was sent to a special school. She had, however, no other symptoms and there had been nothing suggestive of rheumatic fever or chorea.

Examination.—There was slight generalized swelling along the whole length of the fingers, fullness of both dorsal sheaths, 40° limitation of dorsiflexion of the wrists and inability to straighten the fingers. There was no detectable synovial thickening, fluid, or pain, either in the fingers or elsewhere. The spleen was palpable but there was no lymphadenopathy, rash, or nodule formation.

Cardio-vascular System.—The apex beat was of a left ventricular character. There was a systolic thrill in the vessels of the neck and a harsh basal systolic murmur was heard which was well conducted to the apex. There was also a short aortic diastolic murmur. The blood pressure was 150/65. The chest *x* ray showed a prominent left ventricle with a small aortic arch. There was also a bifid fourth rib. Dr. Paul Wood considered that these

findings indicated most probably a congenital aortic lesion.

Laboratory Investigations.—
Erythrocyte sedimentation rate 25 mm./hr (Wintrobe).
Differential agglutination titre for sheep red cells 1 : 32 (positive).

Radiological Examination.—Hands and wrists showed no abnormality.

Biopsy.—The wrist joint showed hyperplasia of the lining membrane with an increase in the number of capillaries, and marked infiltration with lymphocytes and plasma cells, with some polymorphonuclear cells, consistent with rheumatoid arthritis. The dorsal tendon sheath showed similar but more marked changes (Fig. 1).

Diagnosis.—She was thought to be suffering from mild rheumatoid arthritis of the tendinous variety with minimal asymptomatic wrist joint involvement.

Treatment.—She was given wax baths and exercises, and gradually improved during the first 7 months, so that by September, 1952, she was able to resume her normal work though there was still slight limitation of finger extension.

Result.—By June, 1953, no abnormality could be detected, and the erythrocyte sedimentation rate was 19 mm./hr. This improvement is shown in the serial palm prints (Fig. 2).

Case 2.—This girl was first seen in 1950, when aged 12, complaining of inability to straighten the fingers.

When 2 years of age she had developed pain and swelling of the knees and hands, stiffness of the neck, and general malaise necessitating admission to hospital. These signs persisted for about 3 months, but eventually subsided after an attack of measles, leaving no residua.

She remained well until the age of 8 years (1946) when difficulty in straightening the right fifth finger was noted. During the next 2 years other fingers became similarly affected. In March, 1948, she saw her doctor because of tonsillitis and he made a diagnosis of rheumatoid arthritis. Her erythrocyte sedimentation rate was then 45 mm./hr (Westergren). A course of gold injections was stopped after 11 weeks because of the development of a

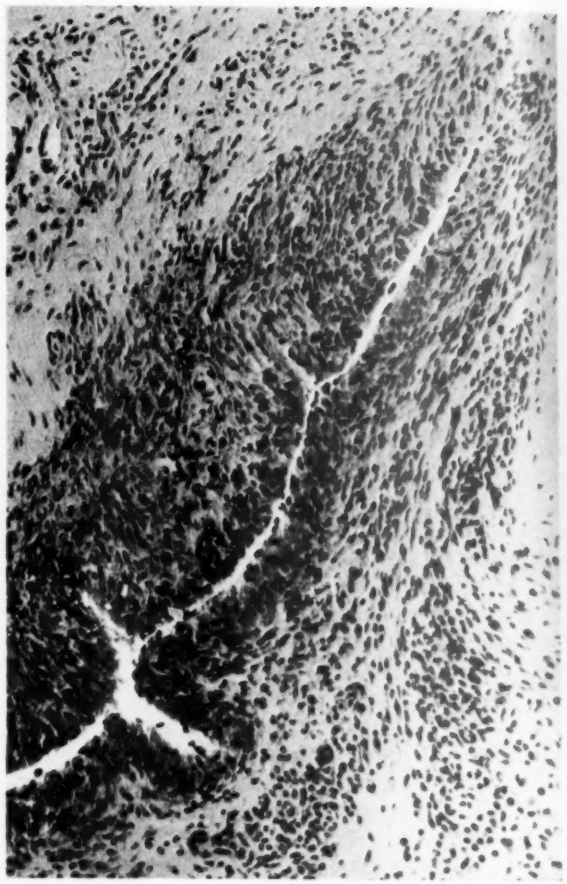

Fig. 1.—Case 1, biopsy of dorsal tendon sheath showing hyperplasia of the lining membrane, increase in capillaries, and marked cellular infiltration.

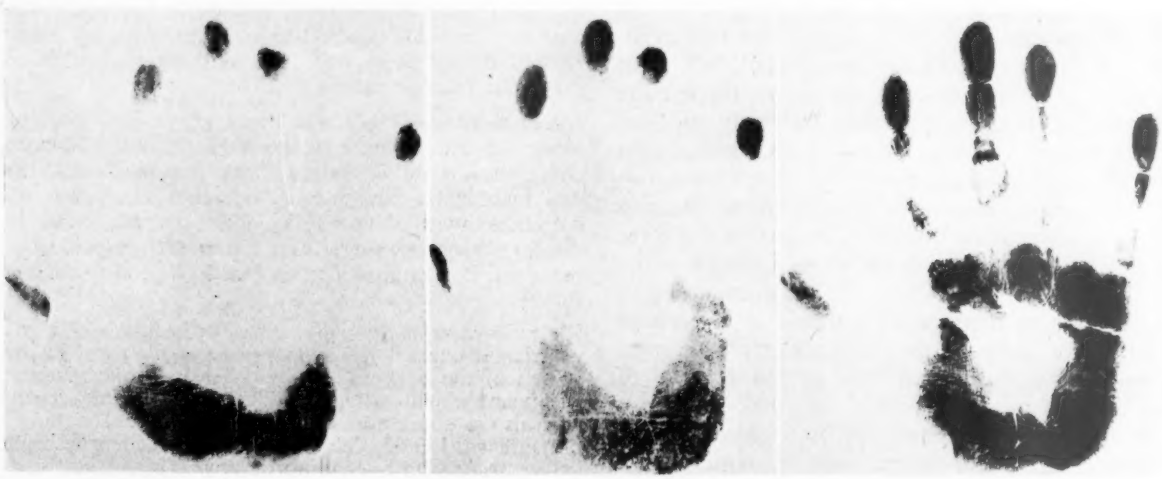

Fig. 2.—Serial palm prints in Case 1, showing improvement.

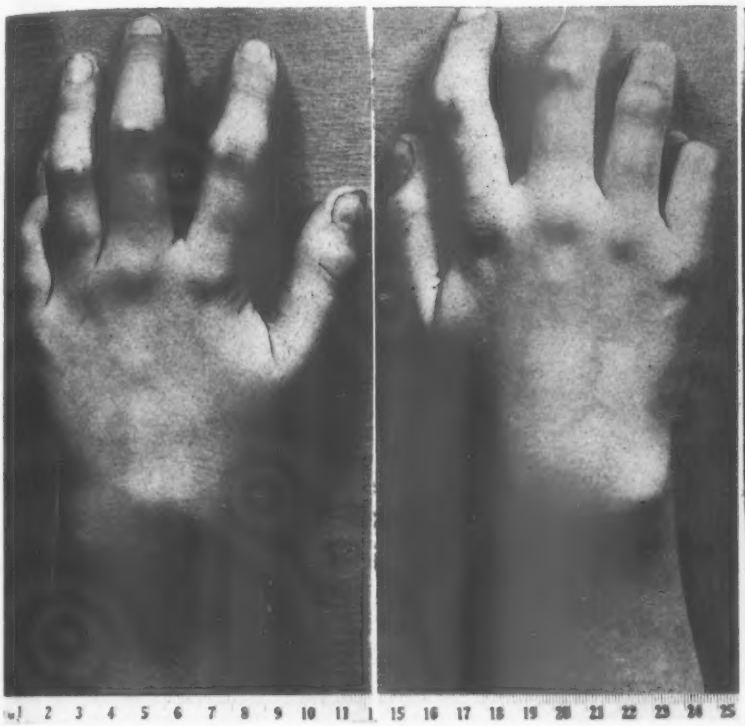

Fig. 3.—Flexion deformities of fingers in Case 2.

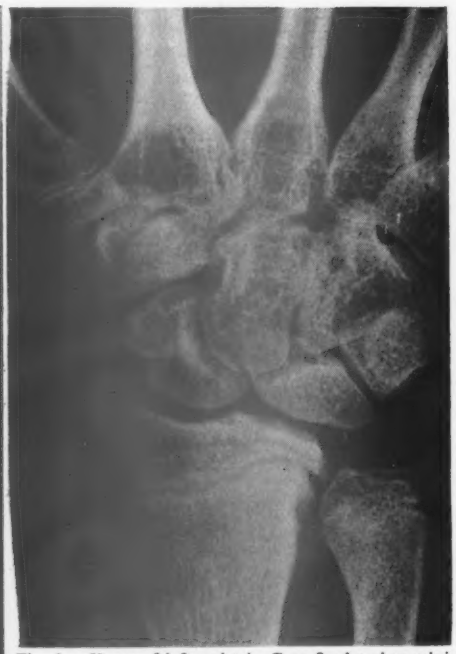

Fig. 4.—*X* ray of left wrist in Case 2, showing minimal healed erosions of carpal and radio-ulnar joints.

rash; it had produced no improvement in the finger contractures, which during the next 2 years appeared to increase. There was no pain at all throughout this period.

Examination.—In June, 1950, she showed limitation of extension of all her fingers with thickening of the tendons in the palms (Fig. 3). In addition there was slight swelling over the flexor tendon sheath on the right internal malleolus. There was no pain, and no evidence of joint involvement, nor was there any lymphadenopathy, splenomegaly, rash, or palpable nodules.

Laboratory Investigations.—

Erythrocyte sedimentation rate 9 mm./hr (Wintrobe).
Differential agglutination titre for sheep red cells was 1 : 2.

Radiological Examination.—Hands and wrists showed some growth deformity of the right and left radial and ulnar epiphyses with minimal healed erosions of both carpi and the radio-ulnar joints (Fig. 4).

Diagnosis.—The patient was thought to have suffered from mild subclinical arthritis of the rheumatoid variety which was now inactive.

Treatment.—Exploration and mobilization of the flexor tendon sheaths of the left hand was done by Mr. Jenkins in October, 1950, at the Postgraduate Medical School, and in May, 1951, a similar procedure was carried out on the right hand. The material removed at operation showed granulomatous infiltration of mesotenon and marked involvement of peritenon with fibrin accretion, palisading, and cellular infiltration. No necrosis was seen (Fig. 5).

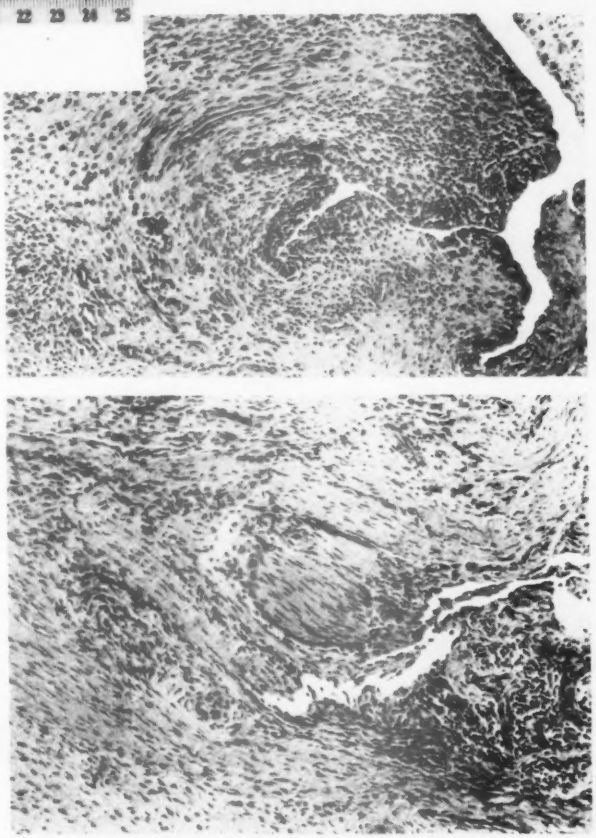

Fig. 5.—Biopsy of tendon in Case 2, showing infiltration of mesotenon and marked involvement of peritenon.

Result.—The operation on the left side was followed by marked improvement in position and ability to use the hand, and this improvement has been maintained to date. On the right, however, although the patient is able to use the hand better, the flexion contractures of the 4th and 5th digits are not greatly changed. This is shown in the serial palm prints (Fig. 6).

Case 3.—This girl was first seen in August, 1952, when aged 12, because of stiffness of the hands.

The onset of the disease was in May, 1952, with swelling and pain in both ankles, which interfered with walking and running. This persisted for 2 weeks, after which there was only slight aching, but one month later she noticed transient pain on using her hands. Shortly after this it was noticed that the fingers would not straighten.

There was nothing relevant in the past history. Her mother had had rheumatic fever for 3 months at the age of 16, but without sequelae.

Fig. 6.—Serial palm prints in Case 2, showing improvement in area of contact (measured in square inches).

Examination.—There was thickening of all the palmar digital tendons with inability to straighten the fingers and pain on full flexion. Both the wrists showed 35° limitation and dorsiflexion, but this was painless. The left elbow was slightly painful on movement and lacked 5° of extension. All other joints including the ankles appeared normal. There were no nodules, lymphadenopathy, splenomegaly, or rash. Other systems showed no abnormality.

Laboratory Investigations.—

Erythrocyte sedimentation rate 20 mm./hr (Wintrobe).
Differential agglutination titre for sheep red cells 1 : 4 (negative).

Radiological Examination.—Hands, wrists, and feet no abnormality.

Diagnosis.—Rheumatoid arthritis of the tendinous variety.

Therapy.—She commenced wax baths and exercises, but the hands did not improve.

Progress.—In October, 1952, she had a severe attack of pain and swelling of the ankles, lasting 2 weeks. By November, the flexion deformity of all the fingers had increased, there was marked nodular thickening in the flexor and extensor tendons of the fingers (Fig. 7, opposite), round the elbow, in the extensor tendons of the toes, and in both Achilles tendons. Apart from limitation of wrist movement all the joints were normal and no other abnormalities could be detected. The patient was admitted to hospital.

Laboratory Studies.—

Erythrocyte sedimentation rate 18 mm./hr (Wintrobe), rising to 20, 25, 37, and 43 mm./hr over the next 6 weeks.
Total leucocyte count 6,000, normal differential.
No L.E. cells present in peripheral blood.
Differential agglutination titre 1 : 4 (negative).

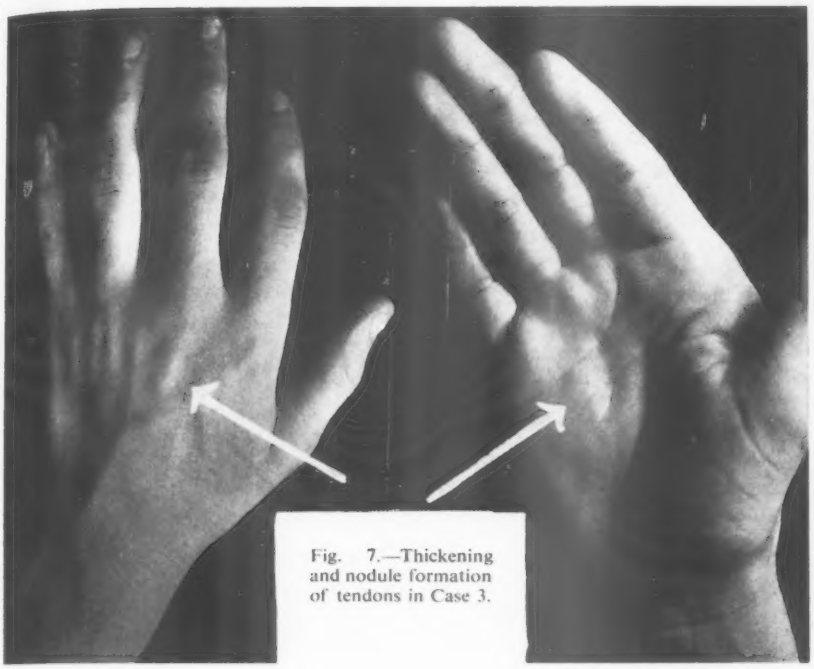

Fig. 7.—Thickening and nodule formation of tendons in Case 3.

Radiological Examination.—No abnormality.

Biopsy.—Left elbow nodule consistent with juvenile rheumatoid arthritis.

Therapy.—She was initially treated by night splintage of the hands and intensive physiotherapy as before, with only a slight improvement. The contractures had now lasted for 5 months, so it was decided to give adrenocorticotrophic hormone. 80 mg. per day for 16 days produced marked improvement in the position of the fingers and decrease of thickening of the tendons (Fig. 8). Despite sodium restriction, fluid retention occurred, and therefore corticotrophin was gradually decreased and stopped

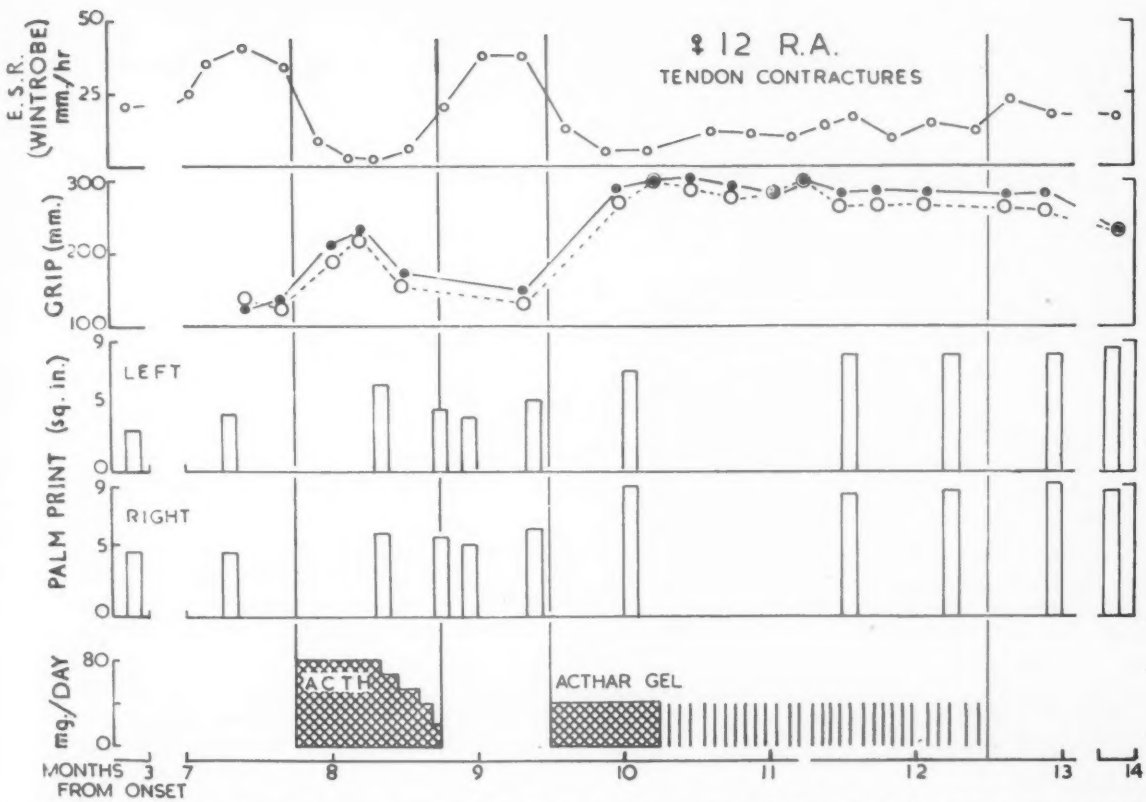

Fig. 8.—Chart showing response to corticotrophin therapy in Case 3. Note improvement initially in area of palm print, grip, and E.S.R. with relapse on cessation of therapy and subsequent remission with a further course.

after a total of 1·7 g. during 30 days. Cessation was followed by a marked increase of nodule formation along both Achilles tendons and round the ankles. There was slight deterioration in the strength of the grips, but little change in the position of the hand. The erythrocyte sedimentation rate, which had fallen to 2 mm./hr, rose to 30 mm./hr (Wintrobe). A second biopsy now taken from the Achilles tendon showed a similar picture to the previous one, except there was slight palisade formation and considerably more cellular infiltration.

Intensive physiotherapy was continued but, as there was no improvement over the following 6 weeks, she was given Acthar gel. In the first 3 weeks, on 40 mg./24 hrs, she rapidly improved, and when the dosage was gradually decreased there was no relapse. The hormone was continued for 3 months, a total of 4·2 g. being given. At the end of therapy there persisted some nodular thickening of both Achilles tendons and one definite nodule of the left elbow. During the period of therapy she had had slight swelling of the dorsal sheaths of both wrists for 5 days, and definite arthritis of the right talonavicular joint lasting 3 days.

Result.—Three months after therapy ended there had been a mild erythrocyte sedimentation rate relapse, but there was no functional disability and no joint involvement, clinically or on radiological examination. Throughout, joint involvement had been minimal and fleeting.

Case 4.—This woman was first seen in 1940, at the age of 24 years, complaining of pain and stiffness of the hands. This had commenced one year previously with pain and swelling of the right index finger, and shortly after of the left index and 5th fingers. In the 2 months prior to attendance she had had occasional pain and swelling of the wrists and hands.

Examination.—In July, 1940, the only abnormality was arthritis of the left 5th proximal interphalangeal and of the left 2nd metacarpophalangeal joints.

Laboratory Investigations.—
Erythrocyte sedimentation rate 20 mm./hr (Wintrobe).

Radiological Examination.—Hand showed no abnormality.

Therapy.—She was treated with wax baths to the hands and salicylates by mouth with definite improvement, so that 3 months later she was symptom-free, but for the first time a nodule was noted on the right 2nd proximal interphalangeal joint.

Progress.—She continued to do full-time clerical work, but through the next 7 years there was a gradual increase in her arthritis and she also noticed development of nodules on the hands. About this time she began to get marked stiffness of the hands and by 1950 she was unable to use her fingers satisfactorily because of nodules in the palmar tendons.

Laboratory Studies.—
Erythrocyte sedimentation rate 13 mm./hr (Wintrobe).
Differential agglutination titre 1 : 128.

Radiological Examination.—Left hand showed a healed erosion (well calcified) and narrowing of the joint space in the left second metacarpophalangeal joint, with reduction of the joint space and cyst formation in the left carpus.

Operation.—The rheumatoid process was thought to be quiescent, and in 1950 the flexor tendon sheaths were incised by Mr. S. A. Jenkins at the Postgraduate Medical School, and free movement of the tendons obtained. A biopsy of the third finger tendon showed fibrinoid necrosis in the wall of the tendon sheath, with considerable cellular reaction mainly of a macrophage type.

Result.—At the time of review in 1953, she felt that her hands had been much improved by the operation, and she had no exacerbation of the arthritis. She showed residual joint changes in the left elbow, both wrists, and both 3rd metacarpophalangeal joints, with some nodule formation along the left big toe and left heel.

Discussion

The tendinous lesions of rheumatoid arthritis, described first by Helweg (1924) from Copenhagen, have been fully discussed by Kellgren and Ball (1950) with particular reference to pathology and treatment. We can agree with those authors on the basis of these and other cases that the dominant change is the appearance of granulation tissue and fibrosis in the mesotenon and peritenon accompanied by necrosis, often fibrinoid, of the tendon fibres or of the granulation tissue and in some instances resembling the ordinary subcutaneous nodule. In the first three cases described above, the contracture was the presenting lesion, and occurred sometimes within 2 months (Case 1) or 6 weeks of onset (Case 3) and sometimes later (Case 2), and either with (Case 3) or without (Cases 1 and 2) nodule formation in the subcutaneous tissues. In the absence of a raised erythrocyte sedimentation rate (Case 2) or raised differential agglutination titre (Cases 2 and 3), it is important to distinguish this type of case from scleroderma. Although the skin appears smooth due to lack of use, it is neither thickened nor bound down; telangiectases are not seen nor is there loss of pulp or bone in the terminal phalanx.

The treatment initially and of early cases is essentially mobilization of the fingers by active and passive movement after wax baths. The excellent results in Case 1 can be easily seen in the serial palm prints. Sometimes it is necessary to use night splints to maintain good finger posture. In a more severe case (Case 3), Acthar gel produced a striking improvement, although the subcutaneous nodule on the elbow failed to disappear. In long-standing cases, surgical action is necessary, and this usually produces an improvement (Cases 2 and 3), although this may not be lasting (Case 2).

Summary

(1) Three cases of rheumatoid arthritis presenting as flexion contractures of the fingers are described.

(2) The histological changes in the tendons are typical of rheumatoid arthritis.

(3) Conservative treatment in the form of physiotherapy and corticotrophin was valuable in the two early cases, whereas, in the third case and in a fourth case also observed, freeing of the tendons by surgical operation greatly improved function.

We wish to thank Dr. Harwood Stevenson and Mr. G. Platt who kindly referred Cases 1 and 3, as well as the other doctors who referred cases to us, and Messrs. P. Fiske and R. Brewer who were responsible for the photographs.

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Contractures digitales dues aux lésions tendineuses comme mode de présentation de l'arthrite rhumatismale

RÉSUMÉ

(1) On décrit trois cas d'arthrite rhumatismale se manifestant sous forme de contractures digitales en flexion.

(2) Les lésions histologiques des tendons sont typiques de l'arthrite rhumatismale.

(3) Un traitement conservateur sous forme de physiothérapie et de corticotrophine s'avéra utile dans les deux premiers cas, tandis que dans le troisième (et dans un quatrième aussi examiné), la libération chirurgicale des tendons produisit une amélioration considérable de la fonction.

Contracturas digitales debidas a lesiones tendinosas como modo de presentación de la artritis reumatoide

SUMARIO

(1) Se describe tres casos de artritis reumatoide manifestándose como contracturas digitales en flexión.

(2) Las lesiones histológicas tendinosas son típicas de artritis reumatoide.

(3) Un tratamiento conservatorio en forma de fisioterapia y de corticotrofina fué útil en los dos primeros casos, mientras que en el tercero (y en un cuarto caso también examinado), la liberación quirúrgica de los tendones produjo una mejoría considerable de la función.

RESTORATION OF KNEE JOINT FUNCTION IN CHRONIC RHEUMATOID ARTHRITIS*

BY

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The restoration of function to the severely deformed knee has always presented one of the most difficult problems to be encountered in the management of patients with chronic rheumatoid arthritis. In the past, the chances of satisfactory functional rehabilitation were so questionable that it became customary to fuse these joints rather than to attempt to restore motion. However, now that cortisone and ACTH are available for use before and after operation, the outlook is more favourable. Irrespective of the place which these hormones finally assume in the therapy for the control of rheumatoid arthritis, there is no question but that they have supplied the surgeon with an important tool. Clinical studies indicate that it is now feasible to perform an operation on these knees extensive enough to correct all the principal pathological features. There is reasonable assurance that the rheumatoid inflammation will be controlled, post-operative scar formation and oedema inhibited, and post-operative pain minimized. The feeling of well-being which frequently results from the use of cortisone or ACTH makes it easier for the patient to co-operate in the post-operative programme which is necessary to complete the functional rehabilitation.

Pathology

This paper is restricted to the consideration of the severely disabled, painful knee with marked permanent deformity and severe limitation of motion. The deformed posture of the knee is fixed by firm contracture of the structures on the flexor side of the joint: the capsule, muscles, fasciae, nerves, vessels, and skin. The structures on the extensor side of the joint are permanently elongated. The marked overstretching of the extensor motor apparatus, which occurs in so many cases, often constitutes a more serious handicap to the restoration of active control than the severe muscular atrophy. Strong periarticular adhesions bind together the structures which must be made to move.

Within the joint there is also extensive adhesion. The suprapatellar pouch may be entirely obliterated. The patella is usually restricted in motion and in many cases it is completely immobilized as the result of firm adhesions which fix it to the articular surface of the femur. Pannus completely covering the articular surfaces is unusual, but in most instances there is some encroachment of fibrous tissue on to the periphery of the articular surfaces. Articular cartilage is missing beneath the pannus or in areas in which scar tissue is attached to the articular surface. The articular cartilage which is preserved is usually thin and fibrillated, but it is rare for the bone to be exposed. The menisci are markedly degenerated or are missing. In some portions of the joint the synovial membrane may be essentially normal in appearance. In other areas the synovia may be considerably thickened and may have the injected appearance of subacute inflammation. It is unusual for the entire synovia to be inflamed.

If severe disability has been present for some years, there may be extensive hypertrophic spur formation at the periphery of the articular surfaces. The periarticular bone is usually very porous and in many instances it is so soft that it is possible to push a blunt instrument such as a haemostat through the cortex of the femur. The articular surfaces of the femur or the tibia are often irregular in contour due to lysis or crushing of the subarticular bone.

Operative Technique

If these joints are to function satisfactorily after operation, the contracted tissues must be lengthened so that the knee can be brought into the position of full extension, the physiological tension of the extensor motor apparatus must be restored so that the joint can be moved skilfully into functional position by active muscular power, and the intra-articular causes of impaired active and passive

* Read at the Annual Meeting of the American Rheumatism Association, May 28, 1953.

motion in the anterior compartment must be eliminated.

For the correction of flexion deformity the posterior capsulotomy operation, reported by Wilson (1929), produces a more satisfactory result than the mere lengthening of the hamstring tendons. In this procedure the biceps femoris tendon and the fascia lata are lengthened and the posterior capsule of the knee joint is stripped from the bone.

To prevent post-operative lateral instability (Preston, 1941), I have modified the technique by stripping the periosteum from the posterior surface of the femur and entering the posterior compartment of the joint from above; only the posterior attachment of the capsule is stripped, so as to avoid injury to the medial and lateral collateral ligaments.

After normal passive extension has been restored, the anterior compartment of the joint is entered to free the structures which glide during movement of the joint. If the suprapatellar pouch, or the joint cavity lateral, medial, and distal to the patella are obliterated, the adhesions are cut and the intra-articular space is re-established. To ensure adequate room in the anterior compartment of the knee, most of the fat pad is usually excised. The irregularities on the articular surfaces and the osteophytes on the patella, femur, and tibia are removed to avoid irritation of the soft tissues which must move over the bones on motion of the knee. In some instances a considerable portion of the articular aspect of the patella is excised, as well as any diseased portions of the synovial membrane.

If the patellar tendon and the quadriceps muscle have become too lax, they are tightened by moving the tubercle of the tibia distally a distance of one-eighth of an inch for every 10° of flexion deformity (Preston, 1940).

After the operation, it is essential to keep the patient under close observation until strong active extension has been restored to the knee and all tendency to flexion contracture has disappeared.

End-Results

Follow-up data are available on eighteen knees of eleven patients upon whom the comprehensive reconstruction operation was done while the patient was under the influence of cortisone or ACTH. The irreversible pathological changes in all these knees were severe, and all the patients were totally disabled before operation. Five of the patients had not been able to walk for some time and the remainder were using crutches. They have since been observed for periods of 6 to 24 months.

Arthrotomy of the anterior compartment of the knee was required in all cases.

Posterior capsulotomy was performed in thirteen knees, but was not required for the correction of the deformity in five knees of three patients.

The flexion deformity of these five knees was slight, varying from 20 to 30°, and when manipulation was attempted before making the incision for the posterior capsulotomy, it was discovered that the deformity could be corrected completely with the use of only mild force.

It was necessary to displace the tubercle of the tibia in seven knees of four patients. In one of these the tubercle was displaced at a later operation when it was discovered that the quadriceps could not be shortened sufficiently to lock the knee in full extension. With one exception, the knees which required the displacement of the tubercle were severely deformed, 50 to 80° of fixed flexion being present.

In evaluating the end-results, a satisfactory result has been regarded as one in which the patient is able:

(1) to do sufficient walking to engage in ordinary activities, with the knee in functional position, without pain;

(2) to flex the knee sufficiently to climb stairs or to get up from a chair.

Some of the patients in the successfully rehabilitated group use a cane for extensive walking, but none of them uses crutches. Five of the patients in this group have had persistent, mild to moderate rheumatoid activity throughout the entire period of observation. Nine of the patients (82 per cent.) had a satisfactory end-result.

The pathological changes in and around the knees of two patients with unsatisfactory end-results were no more severe than in some of those successfully rehabilitated.

One has maintained a satisfactory range of active motion, but the knees have been too painful for more than very limited walking. As she had not been able to walk at all before operation, this result represents an improvement, and the poor end-result seems to be due entirely to our inability to control the systemic rheumatoid arthritis.

The other patient has pain only on extensive walking, but she has practically no motion and there has been a 30 per cent. recurrence of flexion deformity in one of her knees. The systemic rheumatoid arthritis has remained moderately active throughout the entire period of observation, but this has not seemed to be a significant factor in the end-result. The most important cause of the failure to rehabilitate this patient was a marked psychological instability which made it impossible to secure any co-operation in the necessary post-operative muscular rehabilitation programme. As she was unable

to walk before the operation, even this poor result represents some improvement in her situation.

Case Reports

The important features of three representative cases are given below.

Case 1, Female, aged 50 years, had rheumatoid arthritis with generalized joint disability for 13 years and the disease was moderately active continuously during this entire period. When she was first seen, the range of passive motion of the left knee was from 165°-120° (Fig. 1), and the range of passive motion of the right knee was from 165°-110° (Fig. 2). *X* rays revealed narrowing of the intra-articular space, sclerosis of the subarticular bone, and osteophyte formation (Fig. 3). In the rehabilitation of knee joints in which the irreversible pathological changes are severe, complete extension must be restored, but no effort is made to increase the range of flexion beyond 90°. In this case, the limitation of flexion of both knees was severe, but, as there was only mild limitation of extension, open operation was not indicated.

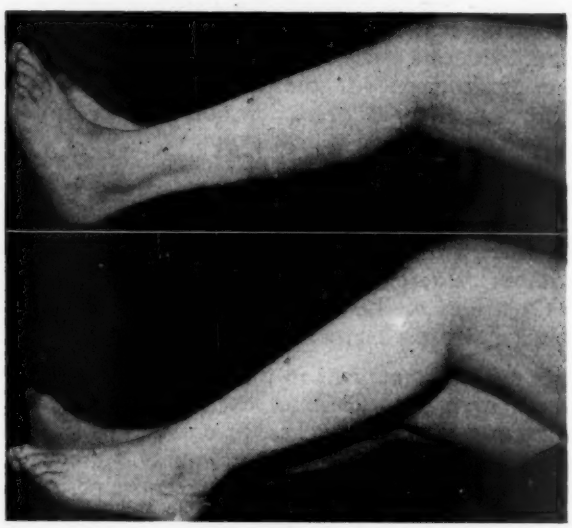

Fig. 1.—Case 1, range of passive motion of left knee before manipulation.

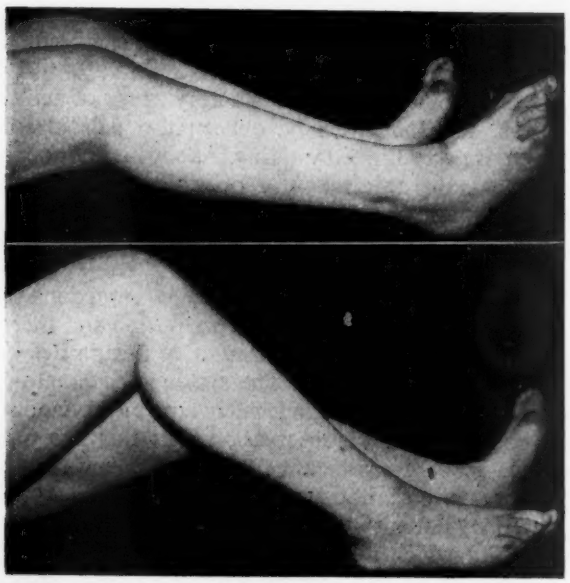

Fig. 2.—Case 1, range of passive motion of right knee before manipulation.

Both knees were stretched into full passive extension under general anaesthesia. Within 2 months the patient developed the ability to bear weight with both knees at the full limit of extension. Flexion of the right knee was possible to 100° and of the left to 90°. At that time there was no more than mild soreness in the knees on prolonged walking.

During the next year the same range of active motion was maintained, but as activity was increased there was a gradual increase of pain in the right knee. The markedly rough crepitation which developed in this knee seemed to be the principal cause of pain, there was no significant pain or soreness in any other joint.

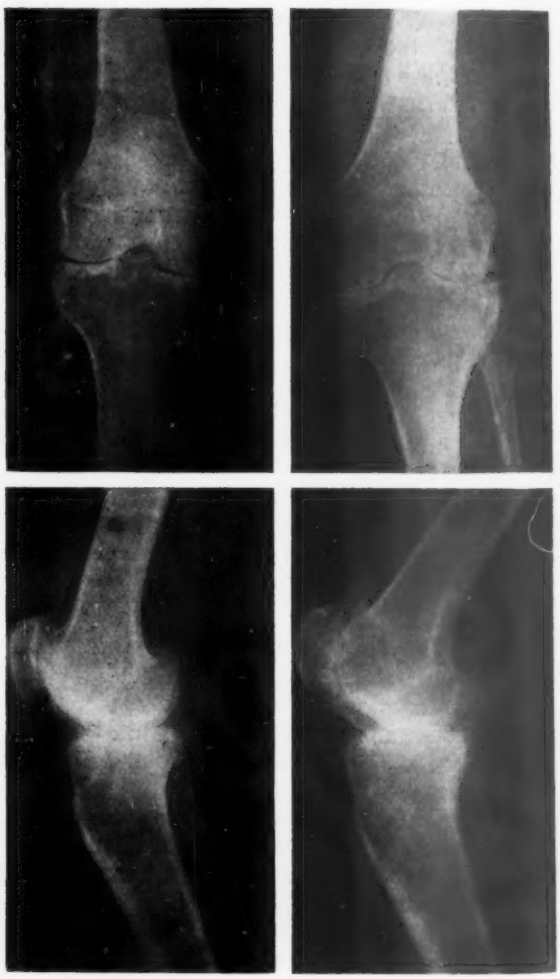

Fig. 3.—Case 1, *x* rays of knee before manipulation.

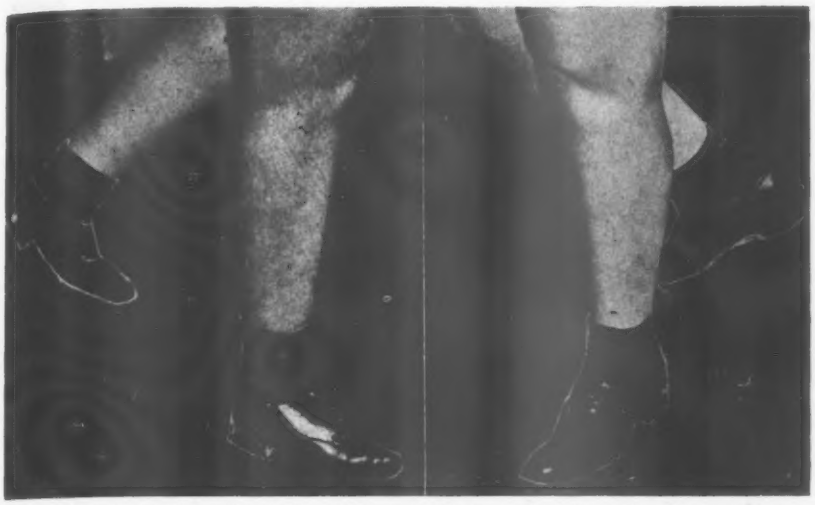

Fig. 4.—Case 1, standing with whole weight supported on one foot, 9 months after operation on right knee.

One year after the manipulations, the anterior compartment of the right knee was explored. The intracapsular space was re-established, the scarred and inflamed portions of the synovia were excised, and the marked bony irregularities on the articular surfaces of the patella and the femur were removed. It was possible to restore reasonably normal contours to the joint surfaces. The knee was immobilized in a cast for one week after this operation, and after 2 months of corrective exercise, the range of active motion of this knee was from 180°-100° without crepitation and with only mild soreness. Fig. 4 shows the patient bearing weight on one foot with the knee locked in extension by active muscular power, 9 months after operation.

At the last examination, 18 months after operation, the range of active motion in the right knee was from 180°-100° and in the left from 180°-85°. Only minimal crepitation was present in the right knee. At that time only slight soreness developed in the knees on prolonged walking. The rheumatoid arthritis remained moderately active throughout the entire period of observation.

Case 2, Housewife, aged 47 years, had rheumatoid arthritis with generalized joint involvement for 13 years before the operation on her left knee. At the time of the operation and during the 2 years of observation after operation, the rheumatoid arthritis was only mildly active. The pre-operative range of passive motion of the left knee was from 140°-90° (Fig. 5).

The operation consisted of posterior capsulotomy, anterior arthrotomy, and transplant of the tubercle of the tibia. After operation the knee was immobilized in a cast for one week, and for the next 3 weeks traction was used when the patient was in bed. Corrective exercises for the quadriceps muscle were started when the cast was removed and these exercises were continued several times a day for 5 months.

Fig. 6 shows the patient bearing all her weight on the left leg 2 years after operation; the range of active motion was from 180°-100°, and there was no pain or soreness even on extensive use of the knee.

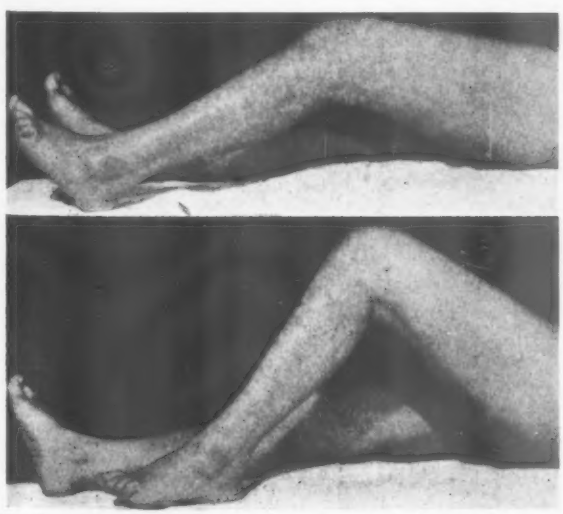

Fig. 5.—Case 2, pre-operative range of passive motion of left knee.

Fig. 6.—Case 2, standing with whole weight on left leg, 2 years after operation.

Case 3, Housewife, aged 50 years, had rheumatoid arthritis with generalized joint involvement for 10 years before operation. For nearly 10 years she has been confined to bed or to a wheel chair because of severe deformities of the knees. The rheumatoid arthritis was moderately active from the onset up to the time of operation. The pre-operative range of passive motion of the left knee was from 100°-30°. The range of active extension was a few degrees less than the range of passive extension (Fig. 7).

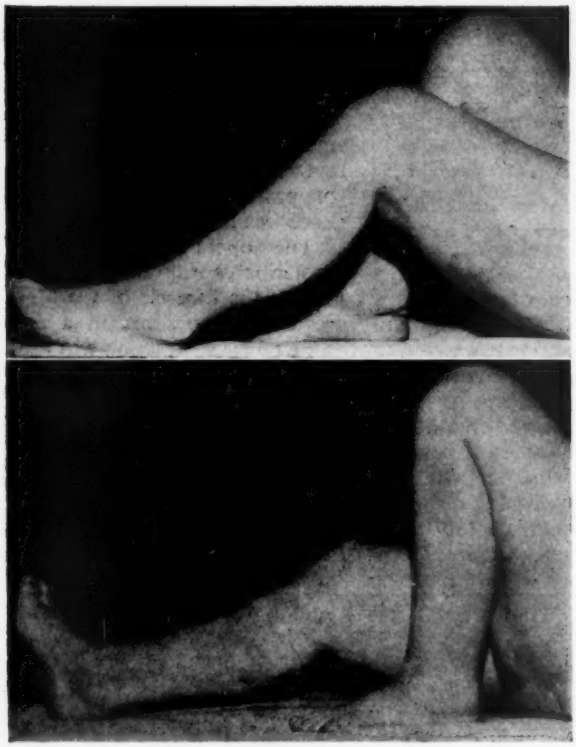

Fig. 7.—Case 3, range of passive flexion and extension of left knee before operation.

She complained of generalized pain of considerable severity at the extremes of motion. Pre-operative *x* rays revealed marked destructive changes in the left knee and only slight bony changes in the right knee (Fig. 8).

Posterior capsulotomy, anterior arthrotomy, and transplant of the tubercle of the tibia were required to restore function to the left knee.

In the right knee there was some chronic rheumatoid pathology, but the principal cause of the flexion deformity was the long-continued fixation of this joint in flexed position which was necessitated by the severe fixed deformity of the opposite knee. The range of passive motion of the right knee was from 160°-40° (Fig. 9). The right knee has not been included in this end-result study as open operation was not required and the deformity was corrected easily by stretching under anaesthesia.

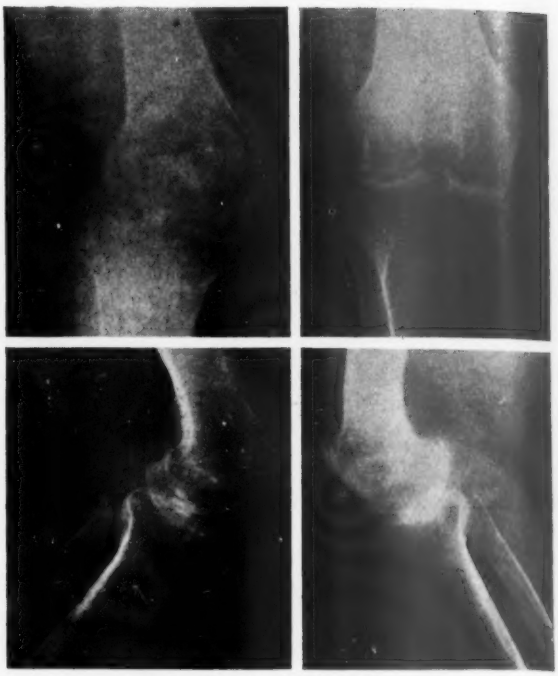

Fig. 8.—Case 3, pre-operative *x* rays.

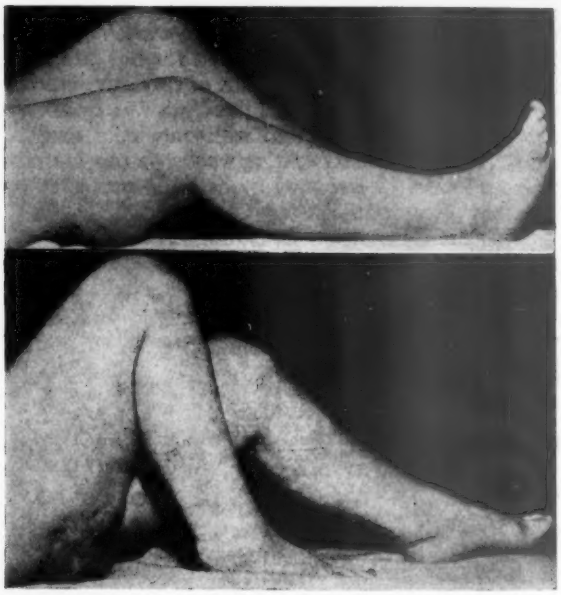

Fig. 9.—Case 3, range of passive flexion and extension of right knee before manipulation.

Casts were applied to both knees for one week after the correction of the deformities. After the removal of the casts, the knees were held in full extension by means of traction until the patient left the hospital. Corrective exercises for the muscles of the hips and legs were performed several times a day.

Fig. 10 (opposite) shows the patient standing on one

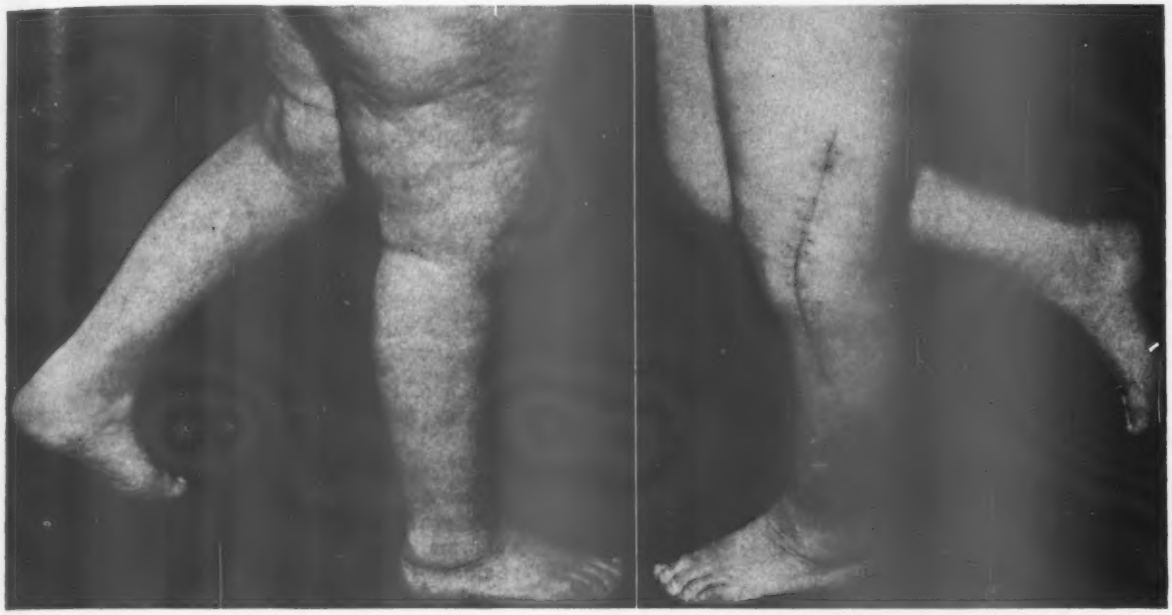

Fig. 10.—Case 3, standing with whole weight supported on one foot with knee locked in functional position, 2 months after operation.

foot with the knee in functional position at the time of leaving the hospital, 2 months after operation.

At the time of the last examination, 6 months after operation, both knees could be locked in functional position by active muscular power. The range of flexion was the same as before operation. There was no synovial effusion in either knee. Mild soreness was still present on extensive use and the muscular strength was still deficient. A cane was used for extensive walking. It was recommended that the corrective exercises be continued and it is expected that muscular endurance will eventually improve so that the cane may be discarded.

Summary

(1) The indications and appropriate operative technique for the reconstruction and rehabilitation of painful knees disabled by arthritis are discussed.

(2) The results of surgical treatment in eighteen knees of eleven patients are described, and three cases are illustrated in detail.

(3) It is concluded that when cortisone or ACTH are used before and after the surgical reconstruction of severely deformed rheumatoid knees, it is feasible to do an operation extensive enough to correct all the principal pathological features.

(4) A satisfactory end-result is dependent upon adequate surgery, control of rheumatoid inflammation, and co-operation of the patient in post-operative rehabilitation programme.

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Rétablissement de la fonction articulaire du genou dans l'arthrite rhumatismale chronique

RÉSUMÉ

(1) On discute les indications et les procédés opératoires appropriés dans la reconstruction et la rehabilitation des genoux douloureux invalidés par l'arthrite.

(2) On décrit et on illustre les résultats du traitement chirurgical de dix-huit genoux chez onze malades.

(3) On conclut que l'emploi de la cortisone et de l'ACTH avant et après la reconstruction chirurgicale des genoux rhumatismaux sévèrement déformés permet de procéder à des opérations d'envergure suffisante pour corriger tous les principaux traits pathologiques.

(4) Le résultat définitif satisfaisant dépend de la chirurgie appropriée, du contrôle de l'inflammation rhumatismale et de la coopération du malade dans les mesures de rehabilitation postopératoire.

Restablecimiento de la función articular de la rodilla en la artritis reumatoide crónica

SUMARIO

(1) Se discute las indicaciones y los procedimientos operatorios apropiados en la reconstrucción y la rehabilitación de rodillas dolorosas incapacitadas por la artritis.

(2) Se describe, con ilustraciones, los resultados del tratamiento quirúrgico de dieciocho rodillas en once enfermos.

(3) Se concluye que el empleo de cortisona y de ACTH antes y después de la reconstrucción quirúrgica de rodillas reumáticas severamente deformadas permite operaciones de envergadura suficiente para corregir todos los defectos principales.

(4) El resultado final satisfactorio depende de la cirugía apropiada, del control de la inflamación reumática y de la cooperación del enfermo en las medidas de rehabilitación postoperatoria.

EFFECT OF ACTH AND SODIUM SALICYLATE ON THE URINARY URIC ACID : CREATININE RATIO, AND CIRCULATING EOSINOPHILS IN MAN

BY

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Since Cochran and others (1950) reported the development of Cushing's syndrome in a 12-year-old girl receiving 5 g. aspirin daily for acute rheumatism, much work has focused on the possibility that the therapeutic and metabolic effects accompanying salicylate administration may be dependent upon the intermediary production of ACTH and/or adrenal corticoids. These authors noted frequent past references to the development of acne and puffiness of the face in patients receiving salicylates for acute rheumatism, side-effects commonly seen during ACTH or cortisone therapy. Referring to their single case, together with the previous work of Reid, Watson, and Sproull (1950), they noted similarities in the effects of salicylates and cortisone not only in the therapeutic response in acute rheumatism, but in their metabolic effects on fluid, chloride, nitrogen balance, and plasma proteins.

Many other reports have since been published on the comparative effects of salicylates and ACTH or cortisone in experimental animals and man. These results may be reviewed according as the changes induced by these two groups of drugs are (*a*) similar, (*b*) dissimilar, (*c*) conflicting.

(a) Similar Changes

(*i*) *Adrenal Ascorbic Acid and Cholesterol.*—Administration of ACTH to rats has been found to decrease the adrenal cholesterol (Sayers and others, 1944a) and ascorbic acid (Sayers and others, 1944b), and the adrenal content of these substances has since been used as a measure of ACTH and cortical activity. Pre-treatment with adrenal cortical hormones protects against this ACTH→depletion effect (Sayers and Sayers, 1947).

Blanchard and others (1950) showed that salicylate caused a significant fall in adrenal ascorbic acid in rats; Hetzel and Hine (1951) confirmed this and showed that the effect was proportional to the dose and that it was inhibited by pre-treatment with cortisone. Van Cauwenberge and Heusghem (1951a) reported depletion of adrenal cholesterol as well as ascorbic acid, and Robinson (1951) showed that this cholesterol depletion occurred within 30 minutes of salicylate administration.

(*ii*) *Urinary Uric Acid Excretion.*—It has been known for many years that salicylates in large dosage can increase urinary uric acid excretion (Byasson, 1877; Sée, 1877; Salomé, 1885), and sodium salicylate has been used to maintain the serum uric acid in gouty patients at normal levels for long periods (Marson, 1953). More recently, ACTH and cortisone have been shown to have uricosuric effects (Thorn and others, 1947b), and the increase in urinary uric acid : creatinine ratio after ACTH injection has been incorporated in a test for adrenocortical function (Thorn and others, 1948). Certain authors, believing that the uricosuric effect of salicylate is mediated *via* the pituitary and suprarenals, have described an intravenous sodium salicylate test for investigation of the function of the two glands (Roskam and others, 1951). The test resembles the ACTH test with the replacement of this drug by sodium salicylate. Creatinine excretion is unaffected by ACTH therapy (Mason and others, 1948), and is stated to be slightly increased by salicylates (Hanzlik, 1927).

(*iii*) *Anti-hyaluronidase Effect.*—Cortisone inhibits the spreading phenomenon (Opsahl, 1949) and both ACTH and cortisone have been shown to inhibit the action of hyaluronidase in causing increased capillary permeability (Benditt and others, 1950). Salicylate has also a definite antidiffusive action (Guerra, 1946; Bertolani and Bergamini, 1950; Schuman and Finestone, 1950; Pelloja, 1952). It does not inhibit hyaluronidase *in vitro* (Swyer, 1948).

(*iv*) *Arthus Phenomenon.*—Salicylates decrease the Arthus phenomenon (Fischel, 1947), as do also ACTH and cortisone (Germuth and others, 1951). All three drugs inhibit tissue reactivity to bacterial antigen in rabbits (Shwartzman and others, 1950).

(*v*) *Serum Arteritis.*—Experimental serum arteritis may be inhibited by both cortisone (Rich and others, 1950; Seifter and others, 1950) and salicylates (Macgregor and Wood, 1950; Sullivan and others, 1948).

(*vi*) *Effects of Hypophysectomy.*—To investigate whether the possible effect of salicylate in stimulating the adrenal corticoids was direct or mediated *via* the anterior

pituitary, various workers have studied the metabolic and haematological effects of salicylate in hypophysectomized animals. Hetzel and Hine (1951) found that salicylate failed to deplete adrenal ascorbic acid in hypophysectomized rats. Van Cauwenberge (1951) confirmed this fact and found that adrenal cholesterol was similarly unaffected. Pelloja (1952) reported that salicylates failed to inhibit the spreading factor in hypophysectomized or adrenalectomized rats.

(b) Dissimilar Changes

(*i*) *Carbohydrate Metabolism.*—Ingle (1941) showed that cortisone could induce severe glycosuria and hyperglycaemia in normal rats fed on a high carbohydrate diet, and ACTH was later found to have similar effects (Ingle and others, 1946). ACTH raises the fasting blood sugar levels in man (Forsham and others, 1948), and the similar effect with cortisone is now utilized in the protection against hypoglycaemia in Addison's disease. Many reports in the last quarter of the 19th century stated that salicylates in large dosage decreased diabetic glycosuria, and for a time these drugs were used in the treatment of this condition (Gross and Greenberg, 1948). Recent reports have shown that salicylates in large dosage reduce the glycosuria of diabetic rats (Ingle, 1950), and lower the blood glucose level (Smith and others, 1952). Smith (1952) showed that the simultaneous administration of salicylates reduced the glycosuric and hyperglycaemic effects of cortisone administered to normal rats fed on a high carbohydrate diet.

Cortisone produces a significant deposition of liver glycogen in rats (Smith, 1952). Salicylate has the reverse effect (Lutwak-Mann, 1942), and also prevents the formation of new liver glycogen by cortisone (Smith, 1952).

(*ii*) *Adrenal Steroids.*—ACTH administration increases the urinary excretion of both 17-ketosteroids and 11-oxysteroids (Mason and others, 1947; Thorn and others, 1947a). Bertolani and others (1951) reported that salicylates increased the urinary output of 17-ketosteroids in guinea-pigs. Van Cauwenberge and Heusghem (1951b) found that aspirin caused an increased urinary excretion of reducing steroids in man, but no constant change in the 17-ketosteroid excretion.

(c) Conflicting Reports

Eosinophil Depression.—Hills and others (1948) first reported a fall in circulating eosinophils after an injection of ACTH and this response has since been used extensively as an index of adrenocortical function (Thorn and others, 1948, 1951). Kelemen and others (1950) reported that single doses of 6-10 g. salicylate induced a significant fall in circulating eosinophils in man, and Bertolani and others (1951) noted a similar eosinopenic effect in guinea-pigs. Meade and Smith (1951) failed to demonstrate any significant change in the eosinophil counts in normal persons within 4 hrs of administration of 75 gr. sodium salicylate. It is noted that this dosage is less than that administered by Kelemen and others (1950).

Roskam and others (1951), however, found that 4-6 g. sodium salicylate did produce an eosinophil depression, but not until between 4-6 hrs. They suggested that the delayed effect resulted from slow intestinal absorption, as 4 g. sodium salicylate induced eosinophil changes within 4 hrs when given intravenously. It is interesting that these authors had shown that the increased urinary uric acid : creatinine ratio reached its peak within the first 2 hrs of giving salicylate orally. Despite this marked difference in time of occurrence, the authors considered that both the eosinophil and uric acid changes indicated stimulation of the suprarenal cortex.

There are, therefore, many similarities in the metabolic effects produced by salicylate in heavy dosage and those produced by ACTH or cortisone, and also a few dissimilarities, notably those affecting carbohydrate metabolism and urinary 17-ketosteroid excretion. These dissimilarities are probably sufficient to negative the hypothesis that the actions of salicylates are dependent upon intermediary production of ACTH. This is supported by the fact that, with the exceptions of acute rheumatism and chronic gout, salicylates compare unfavourably with ACTH and cortisone in the field of therapeutics.

Present Investigations

The following work fails to confirm the occurrence of eosinopenia during salicylate therapy, and suggests that the increased urinary uric acid : creatinine ratio following salicylate administration is unlikely to result from intermediary ACTH production.

Material.—Experiments were carried out on three female subjects, aged 49, 52, and 53 years, who were suffering from osteo-arthritis, rheumatoid arthritis, and gout respectively, and on three male subjects, aged 31, 31 and 32 years, one with rheumatoid arthritis and the other two with gout.

Method.—All subjects were in hospital receiving normal mixed diets together with 3 pints fluid per 24 hrs. No drugs were prescribed before the tests. On test days the subjects remained in bed and their diet and fluid intake was limited to 10 oz. milk at 6, 10 a.m., noon, 2, and 4 p.m. On these days the bladder was emptied at 6 a.m. and thereafter 2-hourly until 4 p.m. The test days were as follows:

(*a*) *Control.*—10 oz. water at 8 a.m.
(*b*) *Sodium Salicylate.*—100 gr. freshly prepared, administered orally in 10 oz. water at 8 a.m.
(*c*) *ACTH.*—50 mg. given intramuscularly at 8 a.m., together with 10 oz. water by mouth.

On test days (*b*) and (*c*), which were separated by at least 3 clear days, the circulating eosinophils were counted just before the administration of the dose and at 9, 10 a.m., noon, 2, 4, and 5 p.m. The counts were made on samples of venous blood by a modification of Randolph's method using *Fuchs-Rosenthal* counting-chambers.

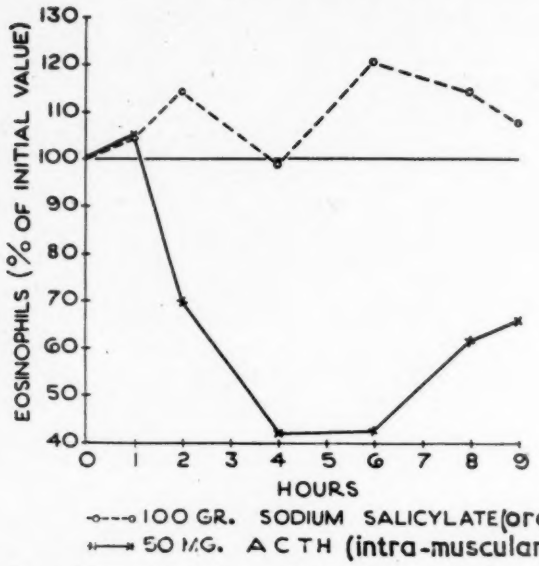

Fig. 1.—Mean values of eosinophil counts in six subjects after administration of:
(*a*) 100 gr. sodium salicylate orally,
(*b*) 50 mg. ACTH intramuscularly.

Fig. 1 shows the results expressed as a percentage of the initial values.

The 2-hr urine samples were tested for uric acid (Brown's colorimetric method, 1945) and creatinine (Folin's method, 1914), and the values have been calculated as uric acid : creatinine ratios. Fig. 2 shows the results expressed as percentages of the initial values.

Additional Experiments.—The above tests, with the omission of eosinophil counts, were each performed twice on a female patient aged 48 years, with severe Simmonds' disease.

She was fit until the birth of her fourth child 13 years previously. Lactation then failed completely and since that time she had noticed complete amenorrhoea, extreme fatigue, mental sluggishness, pallor, and loss of axillary and pubic hair. She had suffered two bouts of unconsciousness and in one of these the rectal temperature had fallen to 86° F. Her appearance was typical of Simmonds' disease, the blood pressure was 100-70 mm. Hg, and the laboratory findings included a urinary 17-ketosteroid excretion of less than 1 mg./24 hrs, a basal metabolic rate of minus 39 per cent., and an insulin tolerance test showing marked hypoglycaemic unresponsiveness.

Fig. 3 shows the effect of sodium salicylate and ACTH

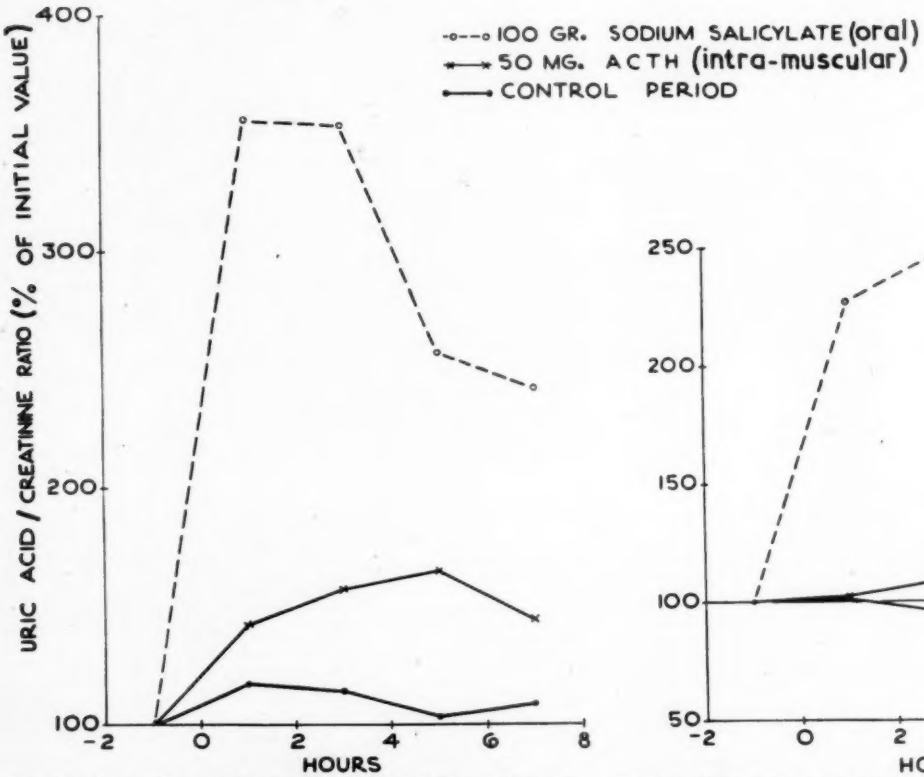

Fig. 2.—Mean values of urinary uric acid:creatinine ratios in six subjects: (*a*) during control period,
(*b*) after 100 gr. sodium salicylate orally,
(*c*) after 50 mg. ACTH intramuscularly.
Results charted at middle of 2-hour periods.

Fig. 3.—Mean values of urinary uric acid:creatinine ratios in a case of Simmonds' disease: (*a*) during control period,
(*b*) after 100 gr. sodium salicylate orally,
(*c*) after 50 mg. ACTH intramuscularly.
Results, charted at middle of 2-hour periods, represent mean of two values.

administration upon the uric acid : creatinine ratios in this patient.

In a further test, three patients (one male aged 31 and two females aged 53), suffering from rheumatoid arthritis, had daily circulating eosinophil counts performed at 10 a.m. and 4 p.m. during a period of 14-15 days. They remained in bed during the test and received a normal mixed diet. No drugs were administered apart from freshly prepared sodium salicylate which was given for a 7-day period in a dosage of 30 gr. at 6 a.m., 2, and 10 p.m. (Fig. 4).

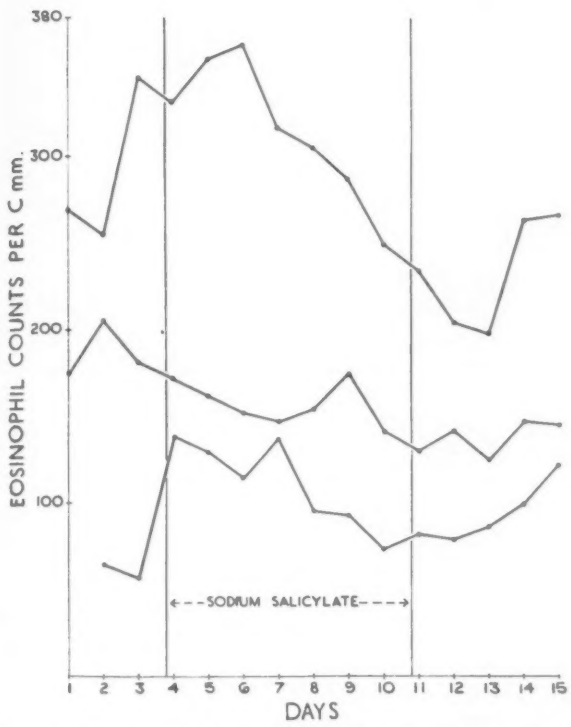

Fig. 4.—Daily circulating eosinophil levels in three subjects expressed as mean of counts performed at 10 a.m. and 4 p.m. During a 7-day period sodium salicylate was administered 30 gr. 8-hrly.

Results

Fig. 1 shows that the ACTH injection (50 mg. intramuscularly) was followed by a depression of the eosinophil level after the first hour, which fell to less than 50 per cent. of the initial value at the 4th and 6th hours. Sodium salicylate administration (100 gr. orally) was followed by an insignificant decrease in the eosinophils at the 4th hour (1·25 per cent. of initial value) and all other counts showed a rise above the initial value.

Fig. 2 shows that ACTH administration was followed by an increase of the urinary uric acid : creatinine ratio, which reached a maximum of 65 per cent. between the 4th and 6th hours, whereas sodium salicylate administration was followed by a maximum increase of 256 per cent. occurring within the first 2 hours.

Fig. 3 shows that while ACTH (50 mg. intramuscularly) was followed by a slight increase in urinary uric acid : creatinine ratio (maximum 15 per cent. at 6-8 hours) in the patient with Simmonds' disease, sodium salicylate (100 gr. orally) was followed by a considerable increase in the ratio (maximum 147 per cent. at 2-4 hours).

Fig. 4 shows that daily eosinophil counts revealed no significant depression in three subjects during a 7-day period in which sodium salicylate was administered in a dose of 30 gr. 8-hourly.

Discussion

The results show that sodium salicylate had a much greater effect on increasing the urinary uric acid–creatinine ratio than ACTH, and acted more quickly. ACTH had the usual effect in depressing the eosinophil count, whereas salicylate failed to depress eosinophil levels during the 9 hours after administration.

If the uricosuric effect of salicylate is dependent upon ACTH production, one would have to postulate its acting far more quickly than 50 mg. intramuscularly ACTH, and producing ACTH far in excess of the equivalent of the 50 mg. given intramuscularly. This being so, it would be difficult to explain why the eosinophils were not more reduced than with the ACTH, more quickly—and certainly within 4 hours, whereas in fact, no depression was observed within 9 hours of salicylate administration. This observation was reinforced by the failure of sodium salicylate (90 gr. daily) to induce a significant eosinophil depression during a period of 7 days.

In the patient with severe Simmonds' disease, one would expect a greatly diminished response to salicylate if its action were mediated via ACTH production. The uricosuric response, however, was well marked, and greatly exceeded that produced by 50 mg. ACTH intramuscularly.

These results indicate that the uricosuric effects of salicylates in man cannot be accounted for by intermediary production of ACTH, and cannot, therefore, be used in the investigation of the hypothalamus—pituitary—suprarenal system as suggested by Roskam and others (1951).

Summary

The literature dealing with the comparative metabolic and haematological effects of ACTH and salicylates is reviewed.

It is shown that the uricosuric action of salicylates in man cannot be accounted for by the intermediary

production of ACTH, and may not therefore be utilized in the assessment of pituitary-adrenal function.

Sodium salicylate failed to decrease the circulating eosinophils either within 9 hours of the administration of a single dose of 100 gr., or during a 7-day period in which 90 gr. were given daily.

I am indebted to Professor A. P. Thomson in whose Department this work was carried out, to Dr. R. Gaddie and Miss Jean Morris for the biochemical data, and to Dr. M. J. Meynell, clinical pathologist, for the eosinophil counts.

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Effet de l'ACTH et du salicylate de soude sur l'acide urique urinaire, le taux de créatine et les éosinophiles sanguins chez l'homme

RÉSUMÉ

On passe en revue la littérature sur les effets métaboliques et hématologiques comparés de l'ACTH et des salicylates.

On montre que l'action uricosurique des salicylates chez l'homme ne peut pas s'expliquer par la production intermédiaire d'ACTH et on ne peut donc pas s'en servir pour déterminer la fonction surréno-pituitaire.

Le salicylate de soude n'a pas réussi à faire baisser les éosinophiles sanguins au cours des neuf heures après l'administration d'une dose unique de 6,5 grammes ni au cours de l'administration quotidienne de 5,8 grammes pendant sept jours.

Efecto de la ACTH y del salicilato de sodio sobre el ácido úrico urinario, la tasa de la creatina y los eosinófilos sanguíneos en el hombre

SUMARIO

Se pasa en revista la literatura sobre los efectos metabólicos y hematológicos comparados de la ACTH y de los salicilatos.

Se demuestra que la acción uricosúrica de los salicilatos en el hombre no se puede explicar por la producción intermedia de la ACTH y que no se puede, pues utilizar para determinar la función suprarreno-pituitaria.

Con el salicilato de sodio no se consiguió la caída de los eosinófilos sanguíneos dentro de las nueve horas que siguieron la administración de la dosis única de 6,5 gramos ni durante los siete días de administración diaria de 5,8 gramos.

COLLAGEN DISEASE COMPLICATING MALIGNANCY

BY

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(RECEIVED FOR PUBLICATION AUGUST 28, 1953)

My purpose in submitting the following six case reports is to call attention to what is, I believe, a significant and little recognized relationship between neoplastic disease and the so-called "collagen" group of rheumatic or connective tissue diseases. The first case, observed in 1946, was so striking that a careful watch was kept for similar cases. The vigil was rewarded over a period of 7 years by another five cases. The case reports have been reduced to a bare minimum—summaries of pertinent positive information—since the object in view is to illustrate the co-existence of two obvious diseases in each patient rather than to prove the correctness of the diagnosis by furnishing a multiplicity of detailed evidence.

Case 1. Male, aged 44, a blind musician, was first seen in the Temple University Arthritis Clinic in June, 1946.

History.—He had had painful joints of 4 months' duration. The arthritis had a rather sudden onset and spread rapidly, so that in a few weeks the shoulders, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints, and knees were involved.

Examination.—Physical examination disclosed the typical findings of rheumatoid arthritis with fusiform swelling, tenderness, limitation of motion, muscle atrophy, and weakness. Other findings included a harsh systolic murmur heard over the whole praecordium, congenital amblyopia, poor nutrition, a chronic cough, and seborrhoeic dermatitis. The erythrocyte sedimentation rate (Cutler) was rapid, the electrocardiogram (by Dr. Hugo Roesler) indicated a primary myocarditis and possible pericarditis with no features suggesting rheumatic fever.

Further Symptoms.—About a month later the patient complained of radicular pain arising from a lumbar segment and of dysphagia. Subsequent studies revealed a carcinoma of the oesophagus with metastases to the lumbar spine and a supraclavicular lymph node. The arthritis, which had been treated by gold therapy slowly improved, but the patient died 1 year from the onset of his arthritis of malnutrition and generalized metastases

Autopsy.—A Grade II squamous cell carcinoma was found with widespread metastases involving the pericardium, pleura, peritoneum, and adrenal. The heart showed advanced myocardosis, thickened and calcified aortic leaflets, and a fibrinous pericarditis.

Comment.—The neoplasm almost certainly preceded the arthritis. The diagnosis of rheumatoid arthritis seems justified from a clinical point of view rather than a diagnosis of rheumatic fever. The rheumatic process appears to be an incident occurring during a rapidly evolving malignant process even though it was at first the outstanding feature of the case.

Case 2. Married female, aged 52, began having symptoms of intestinal obstruction in January, 1946.

History.—A Krunkenberg tumour involving the large bowel with metastases to both ovaries was found 6 months later and a partial resection of the colon and a bilateral oophorectomy were performed. I saw the patient at this time and no articular symptoms or signs were noted. Some months later, the patient developed generalized muscle pain, and, when observed 1 year following her operation, was found to be suffering from a low grade arthritis of the right shoulder, both elbows and knees, and small joints of the hands.

Examination.—Physical examination revealed minimal tenderness and swelling of the affected joints and limitation of motion of the right shoulder. There was a mild chronic ethmoiditis, but otherwise no evidence for focal infection. The rest of the physical examination was not remarkable. The erythrocyte sedimentation rate was 15 mm./1 hr (Cutler).

Therapy.—She was treated with a programme of extra rest, salicylates, testosterone, and local shrinkage of the nasal mucous membranes. In the following 3 months the articular symptoms improved, but the muscle stiffness persisted. She died elsewhere in August, 1947.

Autopsy (performed locally).—Widespread peritoneal metastases were revealed.

Comment.—This case illustrates the appearance of a low grade rheumatoid arthritis occurring during the course of a fatal malignancy. It is possible that the

ethmoiditis and the surgical removal of the ovaries were also factors in precipitating the rheumatic episode.

Case 3. Male, aged 69, suddenly developed, in October, 1949, an erythematous rash on all four extremities, face, neck, and upper thorax.

History.—Generalized stiffness, pain, weakness, and swelling of the musculature followed in a few days. The oedematous features of the illness receded, but the erythematous skin rash persisted and the muscle symptoms became more pronounced. An eosinophilia was noted at this time. The patient was seen by us 3 months after the onset of these symptoms, at which time he had difficulty in swallowing which he related to the upper oesophagus.

Examination.—Physical examination showed an irregular fever up to 101° F., generalized muscle tenderness, multiple doughy indurations involving the skin and muscles, limitation of motion of the shoulders, elbows, hands, and knees, and a patchy erythematous rash resembling in some respects that of disseminated lupus erythematosus. Oesophagoscopy revealed only moderate oedema and narrowing of the upper oesophagus. Pertinent laboratory studies revealed a persistent pyuria and microscopic haematuria. Urological studies disclosed a lesion of the right kidney as the source of the abnormal urinary findings.

Diagnosis.—Dermatomyositis.

Therapy.—The patient was treated with potassium *para*-aminobenzoate, but he responded poorly and succumbed in April, 1950, death being attributed to dermatomyositis.

Autopsy.—A papillary carcinoma of the right renal pelvis was found with metastases to the peri-aortic lymph nodes, a small neurilemmona of the stomach, ulceration of the pharynx, polymyositis of the skeletal musculature, and terminal broncho-pneumonia. The cause of death was dermatomyositis.

Comment.—Although the main clinical feature of this case was dermatomyositis, which ran a 6 months' course and was the immediate cause of death, it is certain that a carcinoma of the right kidney existed 8 weeks after the onset of the illness, and was, in all probability, present well before the onset of the dermatomyositis.

Case 4. Male, aged 36, was admitted to Temple University Hospital in May, 1952, because of infertility.

History.—He had suffered from recurrent episodes of left testicular pain for about 1 year, and was of an allergic diathesis, having suffered periodically from asthma and migraine; 6 weeks before admission he had had an episode of pain and stiffness of the shoulders and hands which persisted and slowly became worse.

Examination.—Physical examination revealed a pale eunuchoid male; there was bilateral limitation of shoulder motion, and swelling, tenderness, and limitation of motion of wrists and fingers. The left testis was moderately enlarged, firm, warm, and tender. The right testis was absent.

Diagnosis.—A clinical diagnosis of atypical rheumatoid arthritis was made and studies were begun to exclude disseminated lupus erythematosus and peri-arteritis nodosa.

Laboratory Studies.—*X* ray of the chest disclosed a large mass in the left lower lobe, which was at first believed to be a metastatic malignancy. Biopsy of the left testis disclosed the histological findings of a malignant seminoma. A search for "L.E." cells revealed 12 per 500 cells counted.

Therapy.—The patient underwent an orchidectomy and was treated by *x* irradiation therapy and nitrogen mustard. Two months later all signs and symptoms of arthritis had disappeared, and when observed 9 months later the patient was gaining in strength and in weight. Subsequent *x* rays of the chest showed no progress of the mass, which is now believed to be of a benign type, unrelated to the malignant seminoma.

Comment.—The diagnosis was malignant seminoma of the left testis associated with disseminated lupus erythematosus with articular manifestations. Unquestionably the neoplasm preceded the "arthritis" in this case.

Case 5. Male,* aged 63, a merchant, was well, except for controlled diabetes, until April, 1953.

History.—He began to have increasing pain in the right knee with subsequent involvement of the left knee and both elbows, and later diffuse pain in the long bones and muscles, most marked in the low back and thighs. When seen by us in August, 1953, he had lost 30 lb. in weight and his diabetes was poorly controlled.

Examination.—Physical examination revealed a supraclavicular lymph node on the right, myopia, tracheal deviation to the left, a firm, nodular, moderately-enlarged liver, swelling and fluid in the right knee, tenderness of both elbows, and minimal flexion deformities of the right elbow and knee with pain on forced extension. The long bones were tender. There was muscle wasting of the right thigh and the interossei. The right patellar reflex and both Achilles reflexes were absent.

Laboratory Findings.—Diabetes, which was quickly brought under control, a large mediastinal mass (probably a bronchogenic carcinoma), which was observed to enlarge rapidly on serial roentgen studies, and a metastatic adenocarcinoma (revealed by a lymph-node biopsy). Alkaline phosphatase elevated (11 Bodansky units), erythrocyte sedimentation rate rapid, serum albumin decreased, cerebrospinal fluid normal. *X* rays of the spine, knees, and long bones showed only moderate osteoporosis and minimal degenerative changes in keeping with the patient's age.

Further Developments.—During his hospital stay there has been a steady decline in his general status. The arthritis became more pronounced. Fluid was aspirated several times from the right knee and compound F instilled with good symptomatic relief.

Comment.—The "arthritis" in this case is indis-

* This case was seen in consultation with Dr. H. Baier.

tinguishable from rheumatoid arthritis. The malignancy almost certainly preceded it, although it gave no local symptoms. Much of the diffuse bone and muscle pain could be explained either on the basis of diabetic neuronitis or as variant of the Bamberger-Marie syndrome. No *x*-ray evidence of bone metastases was found.

Case 6. Male, aged 57, suffered from a Grade 3 squamous cell carcinoma of the epiglottis and larynx, which was irradiated and excised in October, 1952.

History.—Chest *x* ray showed a nodule in the left lower lobe, which increased in size and was biopsied in November, 1952, yielding a histological diagnosis of squamous cell carcinoma, and is presumed to be metastatic from the laryngeal lesion.

In March, 1953, the patient developed arthritis of the left shoulder and by July both knees and ankles were involved, with pain, swelling, local heat, and fluid accumulation.

In June, 1953, the patient had an episode of phlebothrombosis of one leg followed by haemoptysis which was diagnosed as a pulmonary embolism. At this time clubbing of all the fingers began and rapidly evolved.

Examination.—In October, 1953, the erythrocyte sedimentation rate was 36 (Wintrobe), aspirated fluid from the knee showed only 157 white blood cells and the glacial acetic acid test was indeterminate. Culture of the joint fluid was negative. The albumin/globulin ratio and alkaline phosphatase were normal. A search for "L.E." cells revealed 3 per 500 counted.

Comment.—We have here a respiratory tract neoplasm of at least one year's duration (squamous cell carcinoma) complicated by a slowly progressive large-joint arthritis clinically resembling rheumatoid arthritis. The presence of "L.E." cells raises the question of co-existing lupus erythematosus disseminatus as the explanation of the "arthritis". The clubbing would ordinarily be classed as the Bamberger-Marie Syndrome.

Discussion

At this point, the reader will probably suggest that, since both neoplastic disease and the various "collagen" or connective tissue disorders are quite prevalent, their co-existence in six patients could easily be attributed to chance. The chances to be considered, however, are not those of the coincidence of these two types of disease at any time in a lifespan of let us say 70 years, but rather the chance of a rheumatic disease arising spontaneously in the first 6 months or 1 year of a malignant neoplastic invasion. Even with the "chance" explanation thus considerably reduced, I would prefer to offer these cases as illustrative of the co-existence of neoplasm and collagen disease rather than as proof of a causal relation between the two.

However, considerable supporting evidence for such a causal relation is available. One may mention first the subacute type of arthritis not uncommonly found as the presenting symptoms of leukaemia (a type of neoplastic disease) in infants, children, and adolescents.

Furthermore, the association of dermatomyositis with neoplastic disease has been reported in a total of 29 cases (Cottel, 1952; Brunner and Lobraico, 1951; Curtis and others, 1952). Analysis of these reports shows the majority to be cases of carcinoma arising from ovary, stomach, breast, oesophagus, gall-bladder, cervix vagina, rectum, and parotid gland. Other neoplastic processes were retro-peritoneal and endothelial sarcoma of bone, multiple myeloma, Hodgkin's disease, and reticulo-endothelial malignancy, all of which were associated with dermatomyositis.

This suggests that the dermatomyositis was precipitated by some factor common to neoplasia in general. In ten of the above cases the dermatomyositis improved with removal of the tumour and in some instances recurred with regrowth of the tumour.

A recent report by Polley and others (1952) of articular reactions in eighteen of 24 patients suffering from localized fibrous mesothelioma of the pleura states that, while the majority of the articular lesions were attributed to pulmonary osteo-arthropathy, in four instances the findings were similar to those encountered in rheumatoid arthritis. Pulmonary osteoarthropathy and the other articular manifestations subsided after removal of the tumour and recurred when the tumour recurred in three out of the four cases.

Hansen (1952) reports four cases of generalized arthritis with swelling, tenderness, pain, and limited motion of the joints associated with carcinoma of the lung.* In each case the arthritis was the presenting symptom and the lung lesion was discovered on routine chest *x* ray. After resection of the squamous cell carcinoma in three of the cases, the arthritis disappeared promptly and permanently. A subsequent review of one hundred cases of bronchogenic carcinoma by the same author revealed an incidence of 12 per cent. of cases with arthralgia as a presenting symptom.

From the foregoing, I believe we may conclude that there is indisputable evidence for the appearance of certain members of the group of "collagen" diseases during the evolution of a wide range of otherwise unrelated malignant neoplasms. The reversal of the collagen disease following successful removal of the tumours is strong proof that some phase of malignancy bears a causal relationship to the collagen disease. Three cases of arthritis indistinguishable from rheumatoid arthritis, one

* This is not to be confused with pulmonary osteoarthropathy.

case of dermatomyositis, and two cases of presumptive disseminated lupus erythematosus have been cited here. There is suggestive evidence for an allergic diathesis in four of these cases, but it is impossible to know the significance, if any, of this factor.

As to the nature of the relationship one can only speculate. This phenomenon is not due to any one specific type of neoplasm but rather to some unknown factor common to neoplasms in general. Since one feature common to all malignancies is that of invasion, and since the collagenoses can be reversed by removal of the tumour, it seems not unlikely that this phenomenon is related to some factor facilitating the invasion of malignant cells. It may not be too fanciful to assume that the factor in question is a hyaluronidase-like substance which, by entering the general circulation, may interfere with the hyaluronate components of connective tissues and their attending enzymes and co-enzymes. Less likely would be the hypothesis that a malignancy acts as a stressor or as an antigen, or that infection within the neoplasm is the factor. Although this observation of a relationship between malignancy and the collagen diseases cannot at present be fitted into our concepts of the pathogenesis of the collagen diseases, there is little doubt that, if it were understood, it would provide an important step toward understanding the cause of the rheumatic diseases.

From a practical, clinical point of view, the above observations lead to the formulation of the following rule:

When dermatomyositis or collagen disease occurs in middle age without a recognizable precipitating factor, a careful search for malignancy is mandatory.

Summary

Over a period of 7 years, six cases of "collagen disease" (rheumatoid arthritis, dermatomyositis, and disseminated lupus erythematosus) have been seen, which arose in patients suffering from the following types of malignancy:

Carcinoma of the oesophagus,
Krukenberg tumour of the colon,
Carcinoma of the kidney,
Malignant seminoma of the testes,
Metastatic adenocarcinoma and bronchogenic carcinoma,
Carcinoma of the lung.

In all instances the neoplasm preceded the collagen disease, although the presenting symptom in four of the six cases was "arthritis" and the malignancy was at first unsuspected. Four patients were of an allergic diathesis although their allergies were clinically unimportant.

A review of the literature discloses reports of numerous instances of co-existence of malignancy and collagen disease, the most frequent being dermatomyositis, and, less frequently, a form of arthritis clinically indistinguishable from rheumatoid arthritis. This co-existence is believed not to be due to chance, since in many instances removal of the neoplasm was followed by disappearance of the arthritis or dermatomyositis.

The mechanism of this relationship is unknown, but the author suggests that it could be related to some hyaluronidase-like factor secreted by malignant cells which assists their invasion.

These observations indicate that when dermatomyositis or arthritis, or any one of the collagen diseases, occurs in older patients without preceding stress, a careful search for hidden malignancy is mandatory.

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SUMMARIO*

Durante un periodo de 7 annos le autor ha collecte 6 casos del dyscollagenoses (arthritis rheumatoide, dermatomyositis, lupus erythematose disseminate) in patientes suffrente del sequente typos de malignitate:

Carcinoma del esophago,
Tumor Krukenberg del colon,
Carcinoma renal,
Seminoma maligne del testes,
Metastatic carcinoma e carcinoma bronchogenic.
Carcinoma del pulmon.

In omne casos le neoplasmo precedeva le morbo de collageno ben que le symptoma saliente in 4 ex le 6 casos era "arthritis" e initialmente nulle malignitate era suspectate. Quatro del patientes habeva un diathese allergic mais lor symptomas allergic era clinicamente non importante.

Un revista del literatura revela reportos de numerose exemplos del co-existentia de malignitates con morbos de collageno, le plus frequentemente dermatomyositis, minus frequentemente un forma de arthritis clinicamente indistinguibile ab arthritis rheumatoide. Iste co-existentia nos crede, non es accidental, proque in plure casos le excision del neoplasma era sequite per le disparition del arthritis e dermatomyositis.

* This summary is presented by the author in the international vocabulary "Interlingua", which has recently been completed and is being sponsored by Science Service as a translation language for summaries and abstracts. The usual French and Spanish Summaries are given as well for comparison. The Editors of the *Annals of the Rheumatic Diseases* will be glad to receive comments from subscribers of all nations on the intelligibility and usefulness of this vocabulary as an instrument in the international communication of scientific statements.

Le mechanismo per le qual malignitates pote precipitar un morbo de collageno es incognite, mais le autor postula que il poterea esser relationate a alicun factor hyaluronidasoide que es secretate per le cellulas maligne pro adjuvar lor invasion.

Iste observationes indica que quando dermatomyositis, arthritis o alicun del morbos de collageno, occurre in plus vetere patientes sin traumatismo precedente, alora un cerca diligente pro un celate malignitate es mandatari.

Maladie collagène compliquant la malignité

RÉSUMÉ

Au cours d'une période de 7 ans l'auteur a recueilli 6 cas de maladie collagène (arthrite rhumatismale, dermatomyosite et lupus érythémateux disséminé) chez des sujets atteints d'une des affections suivantes:

Carcinome de l'oesophage,
Tumeur de Krukenberg du colon,
Carcinome du rein,
Séminome maligne,
Adénocarcinome métastatique et carcinome bronchogène,
Carcinome du poumon.

Dans tous les cas le néoplasme avait précédé la maladie collagène, bien que dans quatre cas sur six ce fut une "arthrite" qui attira l'attention alors que la malignité ne fut guère soupçonnée. Ces quatre malades présentèrent une diathèse allergique mais leurs allergies n'eurent pas d'importance clinique.

Une revue de la littérature revèle des observations de nombreux cas où la malignité et la maladie collagène coëxistaient; le plus souvent il s'agissait d'une dermatomyosite, moins souvent d'une arthrite indiscernable cliniquement d'une arthrite rhumatismale. On croit que cette coexistence n'est pas fortuite car dans beaucoup de cas l'arthrite ou la dermatomyosite disparaissait après l'ablation de la tumeur.

On ne conna t pas le mécanisme de ce rapport, mais l'auteur admet la possibilité de l'intervention d'un facteur dans le genre de hyaluronidase, secrété par les cellules malignes pour favoriser leur invasion.

Ces observations indiquent que chaque fois qu'une dermatomyosite, une arthrite ou toute autre maladie collagène survient chez une personne âgée sans être précédée par un facteur précipitant déterminable, la recherche soigneuse de la malignité s'impose.

Enfermedad colagena complicando la malignidad

SUMARIO

Durante un período de 7 años el autor ha recogido 6 casos de enfermedad colagena (artritis reumatoide, dermatomiositis y lupus eritematoso diseminado) en pacientes con una de las afecciones siguientes:

Carcinoma del esófago,
Tumor de Krukenberg del colon,
Carcinoma del riñon,
seminoma maligno,
Adenocarcinoma metastásico y carcinoma broncógeno,
Carcinoma del pulmón.

En todos los casos el neoplasma había precedido la enfermedad colagena, aunque en cuatro de los cinco casos una "artritis" fué la primera manifestación sin que al principio se sospechara la malignidad. Los cuatro enfermos presentaron una diatesis alérgica pero estas alergías no tuvieron importancia clínica.

Una revista de la literatura revela relatos de numerosos casos de coexistencia de la malignidad y de la enfermedad colagena, tratándose más frecuentemente de una dermatomiositis y con menos frecuencia de una artritis indistinguible clínicamente de una artritis reumatoide. Se cree que esta coexistencia no es accidental, ya que en muchos casos la artritis o la dermatomiositis desaparecía al extirpar el tumor.

No se conoce el mecanismo de esta relación, pero el autor sugiere la posibilidad de la intervención de un factor del tipo de hialuronidase secretado por las células malignas para favorecer su invasión.

Estas observaciones indican que siempre que una dermatomiositis, una artritis o cualquier otra enfermedad colagena ocurre en una persona de edad avanzada sin que un factor precipitante determinable la precediese, la búsqueda cuidadosa de la malignidad es perentoria.

RHEUMATIC DISEASES IN DENMARK

BY

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From the National Danish Association against Rheumatic Diseases, Copenhagen, Denmark

(RECEIVED FOR PUBLICATION OCTOBER 8, 1953)

In 1946 *The National Danish Association against Rheumatic Diseases* and *The Danish Society for Rheumatology* in co-operation with *Dansk Gallup Institut* conducted a general investigation into the number and nature of rheumatic diseases in the population of Denmark.

Denmark proper, with an area of 42,931 sq. kilometres and a population of about 4 millions, lies in Northern Europe between Lat. 57·7° and 54·6° N. and Long. 8·1° and 15·2° E. The climate is temperate. The mean temperature is approximately 0° C. in January and 16-17° C. in July. The prevailing winds are westerly. Annual precipitation varies from 45 to 80 cm., and the annual number of days of precipitation from 118 to 192.

A country like this is especially suited for an investigation of this nature; it is homogeneous in regard to population, geography, climate, and sanitary and social conditions, and the compulsory notification of diseases is quite comprehensive. Moreover, communications are so good that the country can be covered by a relatively small number of investigators within a very short time. Hospital reports are extensive, and afford good and accurate information, and, owing to the uniform tuition and frequent professional contact between doctors, standards of diagnosis also tend to be uniform.

Material

The investigation covered the whole population of Denmark over 6 years of age, a total of 3,660,000 persons. The patients concerned were divided into three groups:

(A) In-patients.
(B) Disabled patients (receiving public aid).
(C) Out-patients.

The three main subjects of inquiry were:

(1) What is the number of patients?
(2) What rheumatic diseases occur, and what is their distribution?
(3) What do these diseases cost the community in treatment and loss of wages?

The rheumatic diseases were arranged in a few main groups (Table I) without division in smaller groups where nomenclature might be open to doubt or discussion:

TABLE I

INCIDENCE OF RHEUMATIC DISEASE FROM HOSPITAL RECORDS

Type of Rheumatic Disease		(A) In-Patients		(C) Out-Patients			
		No.	Per cent.	Sex		No.	Per cent.
				Women	Men		
I. Articular	(1) Rheumatic fever	1,709	14	3	3	6	0·2
	(2) Rheumatoid arthritis	2,145	18	72	10	82	2
	(3) Spondylosis	407	4	6	10	16	0·4
	(4) Arthrosis coxae	543	5	68	37	105	2·5
	(5) Arthrosis genu	471	4	368	40	408	9·5
	(6) Other arthroses	624	5	—	—	—	—
	(7) Gout	167	1	3	12	15	0·4
	(8) Other articular rheumatic diseases	779	7	107	68	175	4
	Total	6,845	58	627	180	807	19
II. Non-Articular	(1) Neck/head	—	—	463	100	563	13
	(2) Shoulder/arm	490	4	605	194	799	19
	(3) Forearm/hand	—	—	257	71	328	8
	(4) Lumbago/sciatica (mostly disk disorders)	2,027	16	679	324	1,003	23
	(5) Leg/foot	—	—	276	75	351	8
	(6) Other non-articular rheumatic diseases	2,571	22	340	88	428	10
	Total	5,088	42	2,620	852	3,472	81

Results

(A) **In-Patients.**—In 1945, a total of 12,913 patients with various rheumatic diseases were treated in 154 hospital wards and two sanatoria. Of these, 980 were treated at sanatoria; the distribution of the remaining 11,933 hospital patients is shown in Table I (A). The *hospitalized patients* may be classified as follows, according to the frequency of the various forms of rheumatic disease:

Type of Rheumatic Disease (see Table I)	%
(*a*) Undefined non-articular diseases, also termed "muscular rheumatism", presumably mostly psychogenic reactions in connexion with neuroses, climacterium, etc. (II, 6) ..	22
(*b*) Rheumatoid arthritis (I, 2)	18
(*c*) Degenerative diseases, arthroses (I, 3, 4, 5, 6)	18
(*d*) Lumbago/sciatica (II, 4)	16
(*e*) Rheumatic fever (I, 1)	14
(*f*) Other articular diseases, Reiter's disease, ankylosing spondylitis, etc. (I, 8)	7
(*g*) Shoulder/arm (II, 2)	4
(*h*) Gout (I, 7)	1
Total	100

(B) **Disabled Patients.**—Persons receiving public aid in consequence of a rheumatic disease that had reduced their capacity for work to less than one-third of normal were nearly all suffering from rheumatoid arthritis. The number of totally disabled patients was approximately 3,800 (about 5 per cent. of all the disabled in Denmark). This figure is fairly constant from year to year, the increase and decrease being about equal. The annual increase of new invalids is about 365, which is as much as to say that *every day one person becomes totally disabled by rheumatoid arthritis*, the sex ratio being about three women to one man. As a rule, these patients are forced to give up working in about their 45th year; in other words, they lose about 15 normal working years, and each calendar year the community loses 5,500 working years through their disablement.

(C) **Out-Patients.**—This group is by far the greatest and also the most difficult to register, but it is possible to obtain a fairly correct picture of conditions in Greater Copenhagen, since about 80 per cent. of the population have access to six special out-patient clinics for rheumatic diseases, which belong to the Cooperative Sickness Insurance Corporations. The reports from these clinics give a fairly accurate picture of the number, nature, and distribution of rheumatic diseases so treated.

A direct registration was made during the last 3 weeks of June, 1946, and in this period, altogether 4,279 patients with various rheumatic diseases were treated. The distribution of the various types of disease is shown in Table I (C). The *out-patients* may be classified according to the frequency of the various forms of rheumatic disease as follows:

Type of Rheumatic Disease (see Table I)	%
(*a*) Lumbago/sciatica, prolapsed intervertebral disk, spondylolisthesis, disk degeneration (II, 4)	23
(*b*) Painful shoulder, brachial neuralgia, scalenus anticus syndrome, etc. (II, 2)	19
(*c*) Neck/head, occipital-syndrome, cephalalgia rheumatica, etc. (II, 1)	13
(*d*) Degenerative articular disease, arthroses (I, 3, 4, 5)	12·4
(*e*) Undefined non-articular disease (II, 6) ..	10
(*f*) Forearm/hand, epicondylitis, bursitis, etc. (II, 3)	8
(*g*) Leg/foot, restless legs, flat feet, etc. (II, 5) ..	8
(*h*) Undefined articular disease (I, 8)	4
(*i*) Rheumatoid arthritis (I, 2)	2
(*j*) Gout (I, 7)	0·4
(*k*) Rheumatic fever (I, 1)	0·2
Total	100

The sex ratio is about three women to one man. (Table II).

TABLE II
INCIDENCE OF RHEUMATIC DISEASE BY SEX

Sex	Articular Rheumatism		Non-Articular Rheumatism		Total	
	No.	%	No.	%	No.	%
Women ..	627	77	2,620	75	3,247	76
Men ..	180	23	852	25	1,032	24
Total ..	807	100	3,472	100	4,279	100

The total number of patients in Greater Copenhagen applying annually for treatment as out-patients at these special clinics is about 30,000. To these must be added another 10,000 patients, who, not being contributors of any sick insurance fund, apply to private specialists for similar treatment. Therefore approximately 40,000 patients (out of a total of 820,000 inhabitants over 6 years of age) apply every year for special ambulatory treatment for rheumatic diseases in Greater Copenhagen.

The average duration of treatment is about 40 days. Patients with non-articular disease are on an average sick-listed for 20 days, and patients with articular disease for 40 days. The cost of treatment at the special clinics is about $6 per day.

Further General Inquiries

The figures listed above, however, are far from covering the total number of rheumatic patients in Greater Copenhagen. Many do not apply for special

treatment, but get along with such medical and physical therapy as their family doctors are able to give them. Outside the city this class of patients is even larger because specialist treatment is more difficult to obtain. Since this group is not registered, other methods must be used to find its size.

It is not compulsory for doctors to notify cases of rheumatic disease, and the only way to find out the number of sufferers was to approach the patients themselves by means of the Gallup system. By investigating a 1 per cent. section of the population that is representative in regard to sex, age, occupation, etc., 98 per cent. accuracy is obtainable, but to be on the safe side we decided to question about 2 per cent. (a total of 5,661 persons out of 2,840,000). The investigation was carried out in June, 1946, by specially trained senior medical students.

The first question was: *Have you ever had a rheumatic disease?* By means of a system of control questions it could be ascertained whether the diseases complained of were actually recognized rheumatic conditions. It was found that no less than 32 per cent. of the population of Denmark (of 6 years old or over) claimed to suffer from, or have suffered from, a rheumatic disease, and that these diseases occurred most frequently after the age of 45. There was no geographical or occupational differences of any consequence. At the time of the investigation, 761 (13·5 per cent.) out of the 5,661 persons questioned replied *Yes* to the question whether they were suffering from rheumatism then.

In the winter, this percentage is somewhat higher (as may be expected); an investigation in the winter season showed that 18 per cent. of the population were then suffering from some rheumatic disease.

It is interesting to observe that similar results have been obtained both in Great Britain (Kellgren and others, 1953) and in the Netherlands (de Blécourt, 1953), in similar investigations, although the methods of registration were different. This fact is strong evidence that our figures are correct (Table III).

TABLE III
COMPARATIVE INCIDENCE OF RHEUMATIC DISEASE IN GREAT BRITAIN, THE NETHERLANDS, AND DENMARK

Country	Great Britain	Netherlands	Denmark
Percentage of population suffering or having suffered from a rheumatic disease	33-40	—	32
Percentage of population suffering from a manifest rheumatic disease at the moment of registration ..	19	15-20	13·5-18

Conclusions

These figures may serve as basis for a computation of conditions in the whole country; and thence we may calculate the number of sick-days and the number of working years lost in consequence of rheumatic disease (Table IV).

TABLE IV
TIME LOST THROUGH RHEUMATIC DISEASE (days)

Patients	Type of Rheumatic Disease	No. of Patients	% of All Patients	No. of Days Sick
Out-Patients (including 3,800 Disabled)	Articular	216,000	40	4,839,000
	Non-Articular	339,000	60	1,692,000
	Total	555,000	100	6,531,000
In-Patients	Articular	7,200	60	420,000
	Non-Articular	4,800	40	
	Total	12,000	100	420,000
Grand Total		567,000	—	6,951,000

Seven million sick-days a year means that Denmark loses 20,000 working years each calendar year; or, to put it another way, 20,000 persons are idle all the year round because of these diseases.

The rheumatic diseases cost the Danish community a total of $25 *million a year in treatment, loss of wages, and disablement benefits* (Table V).

TABLE V
EXPENSE TO THE COMMUNITY IN TREATMENT, BENEFIT PAYMENTS, AND LOSS OF WAGES (Mill. $)

Patients	Treatment	Loss of Wages	Disablement Benefits	Total Cost
Out-Patients ..	1·74	15·00	—	16·74
In-Patients ..	1·68	1·26	—	2·94
Disabled	—	4·16	0·76	4·92
Total Cost ..	3·42	20·42	0·76	24·60

Summary

The results are given of a survey of the incidence of rheumatic disease in Denmark in the year 1946. Hospital records and disability payments were supplemented by questioning a 2 per cent. sample of the whole population of 6 years old and over.

It is estimated that 13·5 to 18 per cent. of the population are suffering from some form of rheumatic disease at any given moment, and that 20,000 working years and $25 million dollars are lost to the nation annually as a result.

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Maladies rhumatismales au Danemark

RÉSUMÉ

On présente les résultats d'une revue de la fréquence des maladies rhumatismales au Danemark en 1946. Des renseignements provenant des dossiers hospitaliers et des fiches de payement de pension d'invalidité furent supplémentés par un questionnaire direct adressé à une section de la population générale représentant 2 pour cent de tous les individus âgés de 6 ans ou plus.

On estime qu'à n'importe quel moment 13,5 pour cent à 18 pour cent de la population est atteint d'une des formes de la maladie rhumatismale et qu'en conséquence 20 mille années de travail et 25 millions de dollars sont perdus annuellement par la nation.

Enfermedades reumáticas en Dinamarca

SUMARIO

El autor presenta los resultados de una revista de la incidencia de las enfermedades reumáticas en Dinamarca en 1946. A los informes recogidos en los registros hospitalarios y en las hojas de pago de pensión de invalidez se añadió un cuestionario directo dirigido a una sección de la población entera representando el 2 por ciento de todos los individuos de 6 o más años de edad.

Se estima que en cualquier momento entre el 13,5 por ciento y el 18 por ciento de la población sufre de una de las formas de la enfermedad reumática y que en consecuencia la nación pierde anualmente 20 mil años de trabajo y 25 miliones de dólares.

EPIDEMIOLOGY OF RHEUMATIC FEVER IN A RURAL DISTRICT IN ITALY

WITH PARTICULAR REFERENCE TO SOME ENVIRONMENTAL FACTORS

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Scope of Inquiry

The purpose of this research was to ascertain the prevalence of rheumatic fever and rheumatic heart disease in a region of Italy, where the high incidence of both complaints is well known to practising physicians, and to evaluate the weight of some factors generally admitted as important in the pathogenesis of the disease.

Material

The research was carried out in a sample of the population living in a well delimited area of the lower Po valley. The sample was also homogeneous with respect to two other factors: all the subjects were women, and all of them were working as manual labourers. The reason for this selection was to confine the investigation to the incidence of rheumatic fever in a special group of manual labourers, the workers in the rice fields; in Italy these workers are almost exclusively women. A comparable number of women from the same district, but not engaged in the rice fields, were used as controls.

The inquiry (which took 5 months of team-work, from October to February) concerned 930 women, aged 14 to 70 years. The mean age was 34, and the percentage distribution of the cases according to age is shown in the figure. At the time of the investigation, all the subjects were actively pursuing their occupations. The incidence of rheumatic heart disease in this group is therefore referable only to the whole of the active or apparently fit and well population.

The 930 women represented 2·3 per cent. of the total population, and 4·4 per cent. of the female population of the districts where the inquiry took place. The 607 rice workers represented 15·5 per cent. of all the women employed in this way in the districts investigated. The distribution of subjects according to age was almost the same with the rice workers as with the other peasant women (see Figure).

Methods

Investigation.—In each subject this comprised:

(1) *Medical History and Family History.*—Particular attention was paid to rheumatic fever and rheumatic conditions. As definite evidence of rheumatic fever in the past history, we accepted only one or more episodes either of acute migrating polyarthritis, confining the patient to bed for many days, with fever subsiding after salicylates, or of Sydenham's chorea. We considered "atypical rheumatic history" to be that referring only to vague muscular or joint pains, sciatica, stiff-neck, lumbago, etc., without any definite sign of rheumatic activity.

(2) *Clinical Examination.*—Special attention was given to the condition of the heart.

(3) *Screening of Chest*, with orthodiagram of the heart.

(4) *Electrocardiogram*, with Einthoven and unipolar limb leads, and unipolar chest leads $V_{1-2-4-6}$.

(6) *Dark-Adaptation Test*, using the method of Birch-Hirschfeld (1917).

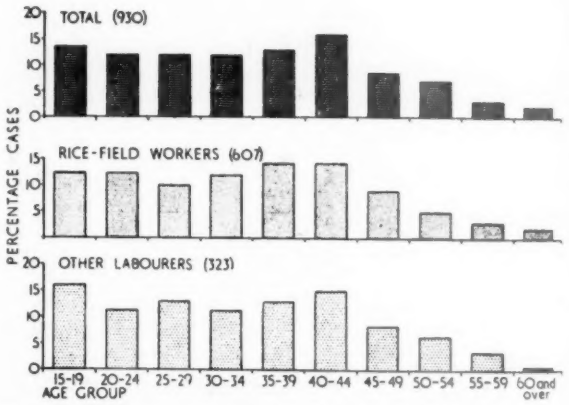

Figure.—Distribution of rheumatic fever in rice-field workers and other labourers by age-group.

Classification of Cases.—In addition to the classification according to occupation (workers in the rice fields and other labourers), the subjects were classified according to:

(*a*) *Medical History.*

(1) Past history of typical acute rheumatic fever or rheumatic chorea.

(2) No such history.

(b) *Results of Clinical Investigation.*
(1) Proved rheumatic heart disease.
(2) Probable rheumatic heart disease.
(3) Possible rheumatic heart disease.
(4) No rheumatic heart disease.

Results

History.—14·9 per cent. of the cases had a history of acute rheumatic fever or rheumatic chorea; and 3·4 per cent. proved to have rheumatic heart disease, without any preceding episode of this kind being recorded. We are unable to give a mean value for the age of onset of the disease, since it was difficult or impossible to get a definite date from the past history in most of the cases. We do, however, consider the observation that the disease began before the age of 35 in 88·4 per cent. of the cases, as reliable. We should like to point out also that, among the cases in which rheumatic fever apparently began later, there were some in which there was little doubt that the onset had occurred at an unusually advanced age (55, 62, and 64 years).

Diagnosis.—Unequivocal evidence of rheumatic heart disease was found in 8·7 per cent. of the 930 cases; it was diagnosed as "probable" in a further 3·3 per cent., and as "doubtful" in a further 6·7 per cent. It was, of course, much more frequently present in subjects with a past history of acute rheumatic fever (35·5 as against 2·3 per cent.).

We were unable to confirm the diagnosis of rheumatic heart disease in more than a quarter of the cases previously so diagnosed (according to the history), and the condition appeared to have been overlooked in 40·7 per cent. of the cases in which we found definite evidence of it. This indicates how commonly a diagnosis of rheumatic heart disease is made which cannot be confirmed by a thorough cardiological examination, and, on the other hand, how often a valvular lesion can remain unnoticed, sometimes, for many years.

Our diagnoses in the 81 cases with valvular lesions are shown in Table I.

TABLE I
DIAGNOSIS IN CASES WITH VALVULAR LESIONS

Cardiac Condition	Percentage
Mitral insufficiency	49·4
Mitral stenosis	24·7
Mitral disease (stenosis and insufficiency)	24·7
Mitral disease and aortic lesions	1·2

The orthocardiogram was of considerable use in the diagnosis of rheumatic heart disease, the heart shadow being completely normal in only 2·4 per cent. of the cases in which the other findings were consistent with this diagnosis.

The electrocardiogram was abnormal in 21·0 per cent. of all the cases studied. Abnormal records were obtained in 79·8 per cent. of cases with a rheumatic history, in 13·4 per cent. of cases with an atypical rheumatic history (history of joint pains, stiff-neck, lumbago, sciatica, etc., without any definite evidence of rheumatic activity), and in 6·9 per cent. of cases without rheumatic history.

The most frequent changes were those indicative of left atrial strain (26·5 per cent. of the pathological electrocardiograms), or of left ventricular strain (25·0 per cent.).

Relation of Incidence of Rheumatic Fever to Other Diseases

(1) *Other Rheumatic Manifestations.*—History of mild arthralgia or myalgia, stiffneck, lumbago, sciatica, etc., was found in 44·7 per cent. of all cases. The frequency of these manifestations was slightly greater in association with a history of acute rheumatic fever (53·6 per cent.) than in the remaining cases (43·2 per cent.); the difference was not statistically significant at the 5 per cent. probability level ($0·1 > P > 0·05$). Signs of osteo-arthritis were seldom observed and occurred almost entirely in the older subjects.

(2) *Other Cardiac Findings.*—A systolic murmur at the apex, apparently classifiable as an "innocent murmur", was found in 4·8 per cent. of all the cases studied. The incidence of this finding was higher (9·9 per cent.) among the subjects who had no history of rheumatic fever, and this supports the view that the finding has no pathological significance.

Hypertensive heart disease was diagnosed clinically in 5 per cent. of the whole series; the average age of the cases with hypertension was 52 years, considerably higher than the average age of the remainder. It must be emphasized that among the subjects over 40 years of age, hypertensive heart disease was significantly more frequent among subjects with a "typical" (5·8 per cent.) or an "atypical" (6·2 per cent.) rheumatic history, than among subjects without any previous rheumatic complaint (2·3 per cent.).

(3) *Correlations with Incidence of Other Disorders.* By the χ^2 test the correlations shown in Table II

TABLE II
CORRELATION OF ACUTE RHEUMATIC FEVER WITH HISTORY OF OTHER DISORDERS

Other Disorders	χ^2
Tonsillar Infections	27·7
Signs of Chronic Tonsillitis	39·2
Previous Upper Respiratory Infection	25·9
Dental Caries	50·5
History and/or Signs of Liver Disease	50·2

were found to be statistically significant, the probability (P) being less than 0·001 in each case.

In addition, significant differences in the frequencies of various other disorders were found when cases with a rheumatic history were compared with the remainder. The disorders in question are shown in Table III.

TABLE III
PERCENTAGE FREQUENCY OF CERTAIN DISORDERS RELATED TO PRESENCE OF RHEUMATIC CONDITIONS

Other Disorders	History of Rheumatic Fever	No previous Rheumatic Complaint
History of Pleurisy ..	35·5	13·6
Alveolar Pyorrhoea ..	13·8	2·7
Diagnosis of Erythema Nodosum in the History*	4·1	0·8

* It is possible that a number of the cases which were said to have had erythema nodosum had, in fact, been suffering from rheumatic fever.

Relation to Family History of Rheumatism

Of all subjects studied 16·6 per cent. had some history of rheumatic fever in a blood-relation. When the subjects had been classified into groups, it was found that there was a rheumatic family history in 20·3 per cent. of subjects with a personal history of acute rheumatic fever or rheumatic chorea, in 16·7 per cent. of subjects with an "atypical" rheumatic history, and in 14·0 per cent. of subjects with no personal rheumatic history. There was thus a highly significant correlation between personal history of rheumatic fever and family history of the disease ($\chi^2=26·7$; $P=<0·005$).

It was also found that 21·3 per cent. of subjects with rheumatic heart disease had a rheumatic family history, while the corresponding figure for subjects with no heart disease was 15·1 per cent.

Of the women studied, 662 had been married. The incidence of rheumatic fever among their husbands was 6·5 per cent. The incidence of the disease among husbands of women who had had rheumatic fever was 10·4 per cent., while that among husbands of women with no rheumatic history was 5·1 per cent. These data confirm the abnormal prevalence of rheumatic fever in the country where the inquiry was performed. The frequent coincidence of rheumatic history in husband and wife demonstrates the importance of common living conditions; the possible role of an infective agent cannot be eliminated.

Effect of Environmental Conditions

(1) *Geography, Climate, and Housing.*—The inquiry was carried out in a region consisting largely of a reclaimed land, very little above sea-level, and rich in water-courses and rice fields. The climate was characterized by long periods of rainy and foggy weather. Housing was generally poor and about one-third of the houses were damp and unhealthy. Subjects with a past history of rheumatic fever were frequently found to be living in damp houses, and a highly significant correlation was obtained between "history of rheumatic fever" and "damp house" ($\chi^2=26·4$; $P=<0·005$). There was no significant correlation between crowded living accommodation and the incidence of rheumatic fever.

(2) *Diet.*—An accurate study of the present diet of the subjects of our inquiry would have been too difficult, owing to the large size of the sample, and owing to its not sufficiently reliable composition. Poor and ignorant country women could not provide data adequate for appraisal of the diet in terms of its caloric value or of its content of individual nutritional factors. Besides, we thought that the knowledge of the total intake of calories, proteins, and vitamins of each subject at the moment of the inquiry was less relevant to the scope of our inquiry than an outline of what had been her alimentary habits during her whole lifetime.

Therefore, the inquiry was necessarily carried out using very elementary questions, as, for instance:

> How often do you eat meat each week?
> Which kind of fat (butter, oil, lard, margarine) is usually employed in your cooking?
> Do you eat fresh vegetables and fruits, throughout the year? and so on.

This part of the inquiry was entirely conducted by a single researcher, in order to secure uniform evaluation of the information obtained. Taking into account the general dietary habits of the Italian people, it was possible to judge, for each subject questioned, whether the dietary intake of carbohydrates (bread, macaroni, rice, potatoes, sugar, etc.), proteins (meat, fish, poultry, etc.), fat (butter, oil, lard), and fresh fruits and vegetables had been "poor", "normal", or "rich". For the purpose of statistical evaluation, these adjectives were translated into arbitrary degrees (1, 2, 3). We may add, incidentally, that the intake of eggs, cheese, and milk (too expensive to be afforded by most of our subjects) had been so scanty, with very few exceptions, as to provide no information useful for our evaluation.

The main observations we were able to make by considering the mean values were that the diet of the studied group was characterized by a considerable excess of carbohydrates and an evident deficiency of proteins, fats, and especially of vitamin-rich foods. Dark adaptation measurements, which suggested that the majority of the subjects were deficient in vitamin A, provided support for the latter finding. A scanty and unbalanced diet was more frequent

among subjects with a history of rheumatic fever than among those with no such history. In particular there was a highly significant correlation between history of rheumatic fever and an inadequate dietary protein intake ($\chi^2=45\cdot4$; $P=<0\cdot005$).

(3) *Working Conditions.*—The importance of factors related to occupation in the aetiology of rheumatic fever and their bearing on the high incidence of the disease in the district investigated is emphasized by a comparison between the workers in the rice fields and the other labourers (Table IV).

TABLE IV
PERCENTAGE INCIDENCE OF RHEUMATIC CONDITIONS IN RICE WORKERS AND OTHER LABOURERS

Rheumatic Complaints	Rice Workers	Other Rural Workers
History of Rheumatic Fever	24·3	6·8
Rheumatic Heart Disease	11·3	2·8
"Atypical" Rheumatic History	17·1	10·8

In addition, it was found that among the rice workers, the incidence of rheumatic fever varied directly with the number of years the subjects had been working in the rice fields. 90·5 per cent of the rice workers who had suffered from rheumatic fever experienced the first attack after they had started working in the rice fields, and in one-third of them the onset of the disease occurred during their first three years in this occupation.

Discussion

The above results allow us to draw certain conclusions with regard to the epidemiology of rheumatic fever.

It is evident that in the district where our inquiry was performed, the incidence of rheumatic fever is extremely high, being comparable only with those reported some years ago in northern countries, as, for instance, in Britain or in New England (Paul, 1943). No enquiries conducted in large Italian towns and strictly comparable with ours are at present available. Nevertheless, the incidence of rheumatic heart disease among school children in Milan (1·7 per cent.; Guglielmini, 1940), and in Rome (1·35-1·7 per cent.; Spolverini, 1939), is very much less than the frequency of rheumatic disease found by us (history of acute rheumatic fever or rheumatic chorea 14·9 per cent.; proved rheumatic heart disease 8·7 per cent.).

These findings agree with the opinion of Puntoni and Tizzano (1948) that rheumatic fever is prevalent in the rural districts of Italy; and with statistics collected in such countries as Hungary (Barath, 1953) and Rumania (Sapira, 1949), where the economic standards of the peasants and their environmental conditions resemble those of the area of our inquiry.

The frequency of a preceding episode of rheumatic polyarthritis in the history of the husbands of the 662 of the investigated women (6·49 per cent.) provides further evidence of the surprisingly high prevalence of rheumatic fever in this region. Poppi, Martinelli, and Abbati (1952) found that acute rheumatic fever was one of the main causes of hospitalization in four general hospitals in the same area, accounting for 1·79, 1·97, 2·4, and 10·8 per cent. respectively of the total number of adults admitted to the medical wards in a period of 5 years.

One possibility to be considered is the genetic factor. The inquiry took place in small villages where the immigration is quite negligible, and where through the centuries, inter-marriage has resulted in some degree of relationship between the majority of the inhabitants.

Several points brought out by our inquiry cast light on the importance of environmental factors.

(1) The geographical and meteorological peculiarities of the area (reclaimed land, very little above the sea-level, rich in water courses, and rice fields, climate characterized by long periods of rainy and foggy weather).

(2) Poverty, the principal reason for unhygienic living conditions (poor housing, overcrowding, scanty and poorly-balanced diet, etc.).

The explanation of the extremely high correlation of "past history of acute rheumatic fever" with "dental caries" or "liver disorders" is probably to be found in common factors favourable to all these conditions: low standards of diet and hygiene.

The whole population in these districts suffer to some degree from the poor living conditions; and the women working in the rice fields are the most exposed. Their economic standard is considerably lower than that of the other labourers in the region; until 20 or 25 years ago they usually started working at the age of 10 or 11 years. They stand long hours in water under a considerable physical strain; most of them migrate seasonally into the rice area and live in badly ventilated and overcrowded barracks, on a poorly-balanced diet.

These unhealthy conditions must have some bearing on the surprisingly high incidence of "rheumatic fever history" (24·3 per cent.) and rheumatic heart disease (11·3 per cent.) among the rice workers. This study, therefore, gives confirmation of the importance of poor living conditions in the epidemiology of rheumatic fever. Many of these adverse environmental factors may be improved or elimi-

nated, and we are glad to say that the publication of the results of the present inquiry caused the Italian Government (1949) to introduce legislation aimed at reducing the risk of rheumatic fever, through a better medical selection in recruiting labourers for the rice fields, and through an improvement in the living conditions of the workers.

Summary

A sample of the population of the rice growing area of the lower Po valley was examined. Of 930 women, aged 14-70, 607 were rice field workers and the other 323 were manual workers otherwise employed.

The incidence of rheumatic fever, rheumatic heart disease, and atypical rheumatic manifestations was found to be 24·3, 11·3, and 17·1 per cent. amongst the rice field workers, as against 6·8, 2·8, and 10·8 per cent. amongst the other workers. There is thus a close connection with the type of employment as well as with poor conditions of life.

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Epidémiologie du rhumatisme articulaire aigu dans une région rurale en Italie (avec mention particulière de certains facteurs d'ambiance)

RÉSUMÉ

On examina un secteur de la population de la région rizière de la vallée de la Po Inférieure. Sur 930 femmes âgées de 14 à 70 ans, 607 travaillaient aux champs de riz et les 323 autres étaient autrement occupées comme manoeuvres.

La fréquence du rhumatisme articulaire aigu, des affections rhumatismales du coeur et des manifestations rhumatismales atypiques s'élevait à 24,3 pour cent, 11,3 pour cent et 17,1 pour cent chez les planteuses du riz, et à 6,8 pour cent, 2,8 pour cent et 10,8 pour cent chez les autres travailleuses. On trouve donc un rapport étroit entre la maladie, le type d'occupation et les mauvaises conditions d'existence.

Epidemiología del reumatismo poliarticular agudo en una región rural de Italia (con mención especial de los factores ambientales)

SUMARIO

Se examinó un sector de la población de la región arrocera en la cuenca del río Po Inferior. De las 930 mujeres entre 14 y 70 años de edad, 607 trabajaron en los arrozales y las demás 323 estuvieron en otras ocupaciones manuales.

La incidencia del reumatismo poliarticular agudo, de la enfermedad reumática del corazón y de las manifestaciones reumáticas atípicas fué de 24,3, de 11,3 y de 17,1 por ciento entre las arroceras, y de 6,8, de 2,8 y de 10,8 por ciento entre las demás trabajadoras. Hay, pués, relación estrecha entre la enfermedad, el tipo de ocupación y las malas condiciones de vida.

INCIDENCE OF REFLEX SYMPATHETIC DYSTROPHY OF THE UPPER EXTREMITY

SHOULDER-HAND SYNDROME

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Heinola, Finland

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According to the large literature on the subject, the reflex sympathetic dystrophy of the upper extremity, or so-called shoulder-hand syndrome (Steinbrocker, 1947), seems to be relatively common. Unfortunately the literature contains no data about the incidence of this disorder as a whole. Many authors have reported its incidence to be 10-20 per cent. of cases of coronary occlusion (Askey, 1941; Johnson, 1943; Järvinen, 1952). Meyer and Biswanger (1942) found it in 39 out of 178 consecutive cases of myocardial infarction. Steinbrocker and others (1948) found an idiopathic shoulder-hand syndrome in six out of 250 cases of painful shoulder.

The aetiology is rather complicated, and several factors have been mentioned, including coronary occlusion (Askey, 1941; Johnson, 1943), trauma (Sudeck, 1902; Leriche, 1937; Nissen-Lie, 1951; Moberg, 1951), spondylosis of the cervical spine (Oppenheimer, 1945), and infections. The aetiology of the so-called idiopathic shoulder-hand syndrome is obscure (Steinbrocker, 1947). All these factors are able to produce the disorder either alone or in various combinations.

According to the even more extensive literature, the "painful shoulder" is also very common, a fact which is confirmed by the experience of the general practitioner.

Material and Methods

To illustrate the incidence of reflex sympathetic dystrophy of the upper extremity, patients attending the out-patient clinic at the Rheumatism Hospital in Heinola was examined, and all cases of painful shoulder and cases with signs of reflex sympathetic dystrophy in the arm were noted.

Altogether 125 patients were selected, and among them were 23 cases (18·4 per cent.) with clearly noticeable signs of reflex dystrophy.

The distribution by age, sex, and (in the 23 cases with reflex dystrophy) by side affected is shown in the Table.

Aetiological Factors

(1) The coronary vessels were affected in four cases.

(2) Osteo-arthrosis of the cervical spine was present to such an extent as to present a possible cause in thirteen cases.

(3) There was a history of preceding trauma in five cases, but in two this was mild and presumably not the cause of disease.

(4) No probable aetiological factors were to be found in four cases in which the diagnosis was idiopathic shoulder-hand syndrome. The proportion of this group to the whole seems to be identical with that found by Steinbrocker.

In one case there have been three subsequent onsets of the disease. This case is one of the group with a history of preceding trauma, and because of its illustrative nature it is reported in detail below.

Case Report

A 77-year-old married female, in 1948 fell on a staircase and injured her back. During the next few weeks, pain, swelling, and limitation of movement developed in the

TABLE

DISTRIBUTION OF CASES OF PAINFUL SHOULDER BY AGE, SEX, AND SIDE AFFECTED

Type of Disorder	Sex		Age Group						
	Male	Female	Under 30	30-40	41-50	51-60	61-70	Over 70	All Groups
Painful Shoulder	31	71	2	12	26	37	18	7	102
Reflex Dystrophy { Right 8, Left 5, Both 10	6	17	—	—	1	14	5	3	23

joints of both lower extremities. She was treated for rheumatoid arthritis, the symptoms subsided within a few months, and complete restoration to normal was achieved.

In 1950 she fell again and was admitted to hospital with a broken femur. No signs of reflex dystrophy developed. During her stay in hospital she developed an acute cholecystitis and was operated on. A few days later, still during her stay in hospital, she developed a typical reflex dystrophy syndrome in the right upper extremity. She was treated with physiotherapy, and in a few months was restored to normal health, with full range of motion in the affected extremity, and no signs of trophic disturbance.

In 1951 she fell again and hurt her left wrist. This was placed in plaster, although there were no signs of fracture. A typical reflex dystrophy developed in the left upper extremity.

When she was last seen in the autumn of 1952, she had severe pain in the hand of causalgic type, with solid swelling of the fingers, hand, and wrist, and limitation of movement in all joints in the hand.

X-ray examination showed marked bone atrophy in the left hand, and slight atrophy in the right.
Erythrocyte sedimentation rate 10 mm.
Blood-pressure 200/110 mm. Hg.
Marked sclerosis in all palpable arteries.
Electrocardiogram showed cardiosclerosis.

Summary

(1) 125 cases of painful shoulder were studied. Of these, 23 (18·4 per cent.) showed typical signs of sympathetic reflex dystrophy of the upper extremity.

(2) These cases of reflex dystrophy came from the older age groups, but the peak of incidence in both types of disorder came in the 51 to 60 year group.

(3) The sex incidence in both types of disorder was about equal (one male to 2·3 females in cases of painful shoulder; and one male to 2·8 females in cases of reflex dystrophy).

(4) Regarding the possible aetiology of the disorder, there were four cases of reflex dystrophy associated with cardiac complication, thirteen with osteo-arthrosis of the cervical spine, and three with trauma. In four cases no aetiological factors were to be found and the diagnosis of idiopathic shoulder-hand syndrome was made.

(5) In one case reported in detail, there were three subsequent onsets of reflex dystrophy during a 3-year follow-up.

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Fréquence de la dystrophie sympathique reflexe de l'extrémité supérieure

(Syndrome "Epaule-main")

RÉSUMÉ

(1) On a étudié 125 cas d'épaule douloureuse. Sur ce nombre, 23 (18,4 pour cent.) ont manifesté des signes typiques de dystrophie sympathique reflexe du membre supérieur.

(2) Ces cas de dystrophie reflexe se trouvaient parmi les personnes âgées, mais la fréquence maxima des deux formes morbides se trouvait entre l'âge de 51 et 60.

(3) La distribution entre les deux sexes était à peu près égale dans les deux formes (un homme sur 2,3 femmes pour l'épaule douloureuse et un sur 2,8 pour la dystrophie reflexe).

(4) Parmi les données éclairant l'étiologie probable de la dystrophie on a trouvé que le coeur était atteint dans 4 cas, il y avait une osteoarthrite cervicale dans 13 cas et un antécédent traumatique dans trois cas. Dans 4 cas on n'a pas trouvé de facteur étiologique et on a fait le diagnostic de syndrome "épaule-main" idiopathique.

(5) Dans un cas suivi pendant trois ans et rapporté ici minutieusement on a observé ultérieurement trois attaques de dystrophie reflexe.

Incidencia de la distrofia simpática refleja de la extremidad superior

(Síndrome "hombro-mano")

SUMARIO

(1) Se estudió 125 casos de hombro doloroso. Manifestaciones típicas de distrofia simpática refleja del miembro superior fueron encontradas en 23 (18,4 por ciento) de ellos.

(2) Estos casos de distrofia refleja procedieron del grupo de edad avanzada pero la mayor incidencia de embos tipos de disturbio encontrose en el sexto decenio.

(3) En ambos tipos de disturbio la incidencia según el sexo fué aproximadamente igual (un hombre por 2,3 mujeres en casos de hombro doloroso y un por 2,8 en casos de distrofia refleja).

(4) Respecto a la etiología probable del disturbio, hubo 4 casos de distrofia refleja asociados con una complicación cardiaca, 13 con una ósteoartritis cervical y 3 con un traumatismo. Ningún factor etiológico fué encontrado en 4 casos y se hizo el diagnóstico de síndrome "hombro-mano" idiopático.

(5) En un caso, relatado detalladamente, hubo tres ataques subsiguientes de distrofia refleja durante tres años de observación.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1953

The annual meeting of the American Rheumatism Association was held at New York, N.Y., on May 28 and 29, 1953, under the presidency of Dr. Currier McEwen of New York. The presidential address, abstracts of the 28 papers and the discussions thereon, and a Panel Discussion of the American Rheumatism Association Cooperative Study of Cortisone Therapy in Rheumatoid Arthritis, with the Report of the American Rheumatism Association Committee which conducted this investigation, are printed below.

PRESIDENTIAL ADDRESS

Plight of Teaching and Research in the Rheumatic Diseases

by

CURRIER MCEWEN

President, American Rheumatism Association,

1952-53

Dr. Ragan, members, and guests of the American Rheumatism Association: When I say that I have attended these meetings of our Association for 22 years and have missed only three—and those unavoidably during World War II—I think you will accept my deep interest in the American Rheumatism Association. You will appreciate, therefore, how much your action in electing me your President has meant to me. I have been grateful for, and frankly proud of, the honour you have done me, and I have thoroughly enjoyed the various activities of the past year, which have brought me, as President, more intimately in touch with the association and its work than ever before.

As we look back over the 23 years since the American Rheumatism Association was founded, we have reason to be pleased at the progress made in the study of the rheumatic diseases and at the part the Association has played in stimulating it. If we consider the record objectively, we shall have to acknowledge that some of the papers and a fair amount of the discussion at the early meetings were far closer to empiricism than they were to science, and only in rheumatic fever were the quality and quantity of research strong. Now—and today's programme illustrates the point—research in the rheumatic diseases can take its place beside that in the other major fields of medicine; and comparable advances have been made in the care of patients and in the appreciation of the social, economic, and public health significance of arthritis and rheumatism.

While we contemplate with justifiable pride the advances which have been made, we must, however, accept the sobering realization that this progress has been too much dependent on far too small a number of individuals. Our whole membership, which includes most physicians in the United States who have a special interest in the rheumatic diseases, totals less than 800, or approximately one to each 165,000 of the population, and one to each 12,000 of the nation's victims of these diseases. Moreover, the facilities and the skills necessary for first-class clinical and laboratory investigations in arthritis and rheumatism are woefully inadequate. This is a deficiency which can be easily overlooked because of the quality of much of the work which has been done, but even the most cursory comparison with the research opportunities in other branches of internal medicine shows how true it is.

The crux of the matter is that, although the quality of work in the rheumatic diseases has improved enormously in the past 23 years, the number of trained workers has increased very slowly. I think it is fair to say that few of us realized this deficiency until comparatively recently when two factors combined to dramatize the situation: the first of these, which our Association and the Arthritis and Rheumatism Foundation played a major role in bringing about, was the awakening of public concern over this group of diseases which cause such untold suffering and economic loss; the second, which stemmed naturally from the first, was the creation of funds for the support of research in this field. Immediately, it became apparent that the experienced investigators required to carry out the research so urgently needed do not exist in sufficient numbers. It is to the explanation of this situation and to its solution that I wish to devote the remainder of these remarks.

Primarily, I believe, the cause can be traced to our medical schools, for in not more than half a dozen of them is the number of full-time faculty members devoted to the study of rheumatic diseases comparable to that which would be expected for work in other important diseases such as cancer, diseases of the heart, nephritis, and the like. In many schools very capable men are caring for patients, teaching, and carrying out clinical studies on a part-time basis; but in modern medical education it is the full-time faculty member who influences the student most, just as it is the full-time man who attracts research grants. Thus, the eager, young, potential investigators in student bodies throughout the country make scientific attachments as undergraduates or as interns which lead them to careers in cardiology, hypertension, diabetes, and other branches of internal medicine in their later years, but rarely to careers in the rheumatic diseases.

One may well ask why it is that the rheumatic diseases have so few full-time disciples among the faculties. The answer, I believe, is easily found if one considers the development of modern American medical education. As the period of the proprietary schools came to an end and funds began to be available for medical schools through their parent universities, the first departments to be developed were those of the basic sciences. Only much later did similar support become available for the clinical departments, and the meagre funds at hand were, quite naturally, used to exploit those fields of internal medicine which were currently important, such as the infectious diseases, which the work of the French and German bacteriologists had placed on a scientific basis, and cardiology, which was flowering under the stimulus of the English and Dutch physiologists and clinicians. Little by little, as the budgets of medical schools expanded, a nucleus of full-time men took their places in the departments of medicine; and, of course, the fields from which they were recruited were those of current scientific advance and interest. Unfortunately, the rheumatic diseases have been late in reaching scientific maturity. The reasons are many, but the practical point of the matter is that now, when one might expect to see the gradual development of the rheumatic diseases as a major component of the country's departments of medicine, the budgets of the schools are so strained that the addition of personnel and facilities through university support is a very remote possibility. In the course of time, as vacancies develop in teaching staffs, one can now expect that a reasonable share of the places will be filled by men with special interest in the rheumatic diseases. This process, however, will require many years before it begins to pay dividends in the form of a rapid increase in the number of investigators and clinicians.

I submit that the only possible answer lies in the provision of new funds to support the work of the medical schools in the rheumatic diseases. Ideally this would be in the form of gifts to endow salaries and to construct the vitally needed laboratories. Unfortunately, however, gifts and bequests of the size required are unlikely to solve the problem in very many institutions. In this situation it is earnestly to be hoped that Congress will appropriate the funds needed to enable the United States Public Health Service to make teaching grants and construction grants in the field of arthritis and rheumatism. Such grants have been of incalculable benefit in cancer, diseases of the heart, and mental diseases, in which at least moderately adequate facilities already existed. They would be of even greater benefit in the case of the rheumatic diseases, because of the great lack of existing teaching funds and laboratory facilities in that field. The grants in aid of research, the traineeships, and the fellowships which the National Institute of Arthritis and Metabolic Diseases, the Arthritis and Rheumatism Foundation, the Masonic Foundation for Medical Research and Human Welfare, and other agencies have provided in recent years have been of the greatest aid. In addition to these forms of support, however, there is urgent need for teaching and construction grants to the medical schools if we are to overcome the present bottleneck of insufficient numbers of young physicians entering the ranks each year to carry on the fight against these diseases which are the greatest cause of disability in our nation to-day.

The Use of Plastic Materials in the Splinting of Arthritic Patients. By MILTON C. COBEY, *Washington, D.C.*

During the last 3 years, with the aid of the Mellon Institute in Pittsburgh, and the Walter Reed General Hospital, it has been possible to develop various substances known as "Orthoply", "Orthoroc", "Melmac", and "Melamine" from various resins. These resins have been used in conjunction with various types of cloth, such as glass cloth, ordinary cotton, felt, and finally with plaster-of-paris, to make waterproof types of moulds, shells, and half-casts that can be applied directly to the patient to be worn for many months; they can be made very light and thin, both flexible and rigid, as may be required. Their use with arthritic joints in putting the joints at rest has been a great help because they are easily made, and inexpensive, and actually, in the case of "Melmac 405", require less plaster-of-paris than normal casts. These give excellent half-casts or whole casts which do not go to pieces when made wet by the bath or by urine, and they can be worn for long periods, both in and out of bed. Because of their lightness they do not inter-

fere greatly with the patient's functions, and they can be used on any extremity or as hip spica or body casts.

It is now possible to have plastic bandages ready to apply directly to the patient without any additional steps. These bandages are soaked in water and applied either in splints, or as rollers; they harden in the same length of time, but with three times the strength of ordinary bandages; they are completely waterproof in every respect, are cool and light, and may be worn during physiotherapy treatments and other activities to restore function.

Discussion.—DR. JOHN NORRIE SWANSON (*Toronto, Ont., Canada*): I think the committee and Dr. Cobey should be congratulated for taking first things first. No matter what other treatment we have for arthritis, the protection of the joint and correction of the deformity are still the most important things.

We have had some experience with "Melmac", although not as much as we should like. There appear to be two disadvantages in its use: first, it is expensive and not economical to use in small amounts, for once a can has been opened, the contents do not keep, so that a whole can is expended into the making of one small hand splint; secondly, it is sticky and will clog pipes and drains in the plaster room.

Until it is readily and more cheaply available for use we prefer to use nylon casts. Ordinary plaster-of-paris casts are made and then painted with liquid nylon, which renders them waterproof and washable. They are exceedingly light, a hand cast weighing less than 3 oz. Usually the nylon paint is coloured (pink, blue, green, or yellow), and this makes the casts more attractive to the patient. They are fitted with webbing straps and self-adjusting sliding buckles, so that they can be put on and taken off very quickly. For example, one leg cast was worn for more than a year and the patient could slide it on and off in 7 seconds.

The formula for the nylon paint is: nylon flake 85 parts by weight, alcohol 15 parts by weight. This solution is simple to prepare and lasts for some time without deteriorating. The cost of a hand splint may be as little as 25 *cts.*

DR. COBEY: I should like this idea of nylon paint, but in 1936 I had an exhibit at the meeting of the American Medical Association in Atlantic City, demonstrating plaster casts painted with celanese acetate mixture, which is very similar to nylon. We gave it up because the cast cracks, the water gets underneath the nylon, or the paint, and the cast dissolves.

I should like to take issue also with the comment about "Melmac" clogging drains. To my knowledge, except when three or four pounds of "Melmac" are poured down the drain, it never clogs, and I had a report from the manufacturers of only one clogging in their own laboratory.

The last thing I want to say is that the new bandage I have announced this morning is so made that we find no residue in the water bucket. We cannot go into the chemistry of it, but when the new bandage comes out, there will be no residue whatsoever and there will be no loss of plaster-of-paris or "Melmac" from the bandage.

Reconstruction of the Knee Joint in Chronic Rheumatoid Arthritis. By ROBERT L. PRESTON, *New York, N.Y.*

The restoration of function to the severely deformed knee has always presented one of the most difficult problems encountered in the management of patients with chronic rheumatoid arthritis. In the past the end-results of treatment were uncertain, for when extensive surgery was done to restore motion, the functional improvement secured at operation was frequently lost through the development of excessive post-operative scar in and around the joint or the exacerbation of the rheumatoid inflammation. The chances of satisfactory functional rehabilitation were so uncertain that it became customary to fuse these joints rather than to attempt to restore motion. However, now that cortisone and ACTH are available for use before and after operation to inhibit scar formation and control the rheumatoid inflammation, the outlook is more optimistic. When these hormones are used an operation can be done which is extensive enough to correct all of the principal features of the pathology, and it has been demonstrated that it now is possible in a high percentage of cases to restore and maintain motion through a functionally useful range.

If these joints are to function satisfactorily, sufficient passive motion must be restored to permit the knee to be brought into the functional position of full extension, the motor apparatus must be restored so that the joint can be moved skilfully into a functional position by active muscular power, and the intra-articular causes of impaired active and passive motion in the anterior compartment must be corrected. In the average case, all three aspects of the mechanical derangement are corrected at the operation.

Twenty-four knees of fourteen patients were subjected to the comprehensive reconstruction operation while the patient was under the influence of cortisone or ACTH, the end-results after a follow-up period of 6 to 36 months are described.

Discussion.—DR. JOHN G. KUHNS (*Boston, Mass.*): Dr. Preston has asked me to comment on this paper, a very interesting piece of work on the rehabilitation of knees with limitation of motion. It brings out a number of problems. When we open the anterior compartment of the knee joint, there are two possible solutions, depending upon the amount of surgery that we perform. If our surgery is mild, such as removal of fat pads or of semilunar cartilages (if they are diseased) and a few small spurs, nothing further is required, whether we use cortisone or not. If very extensive surgery is needed, the problem of adhesions arises. Frequently, even in the presence of cortisone, adhesions will develop and motion will be greatly decreased. In the posterior compartment, of course, this problem is not so important. We have seen very few patients in whom we have done a precedure similar to that described by Dr. Preston who developed any limitation after operation.

In many respects we have found that hydrocortisone injected just before the manipulations is even better than cortisone. We are doing less and less manipulation; the physiotherapist does it now, usually with a more vigorous exercise programme.

I should like to ask Dr. Preston what his dosage of cortisone is, and how long he continues it post-operatively?

DR. PRESTON: The dose of cortisone is usually 100 mg. per day, one week before and 3 weeks after operation.

In all these cases the final authority on how the cortisone will be used is the rheumatologist, but I think that gives the maximum effect as far as surgery is concerned.

Progressive Systemic Sclerosis (Scleroderma). By THEODORE B. BAYLES, PAUL M. BEIGELMAN, and FRED GOLDNER, *Boston, Mass.*

The skin manifestations of scleroderma have long ago been recognized and adequately described. Since 1897 the systemic nature of the disease has been known, but it is often reported only by specific system involvement.

Data concerning skin and constitutional symptoms, Raynaud's syndrome, cardiac and lung involvement, gastro-intestinal symptoms, and life course are presented for fifteen patients, twelve females and three males. The clinical laboratory findings of anaemia, raised sedimentation rate, reversal of albumin-globulin ratio in five, and low vital capacities will be discussed. Thorough radiological studies in nine cases revealed evident multiple systemic involvement visible in eight patients.

Fourteen patients had electrocardiographic studies. Non-specific but frequent T wave inversions, prolongations of the Q-T interval, low electromotive force, and various arrhythmias were seen. The advanced sclerodermatous myocardial changes demonstrated in two cases are correlated with autopsy findings. All five autopsied cases exhibited diffuse pathological systemic involvement.

A long list of treatments was used without much result. Nine of the patients had ACTH and/or cortisone therapy: eight had only mild transient benefit but one patient has been on maintenance cortisone therapy for more than 30 months with apparent consistent benefit.

The pathological findings are related to those in other "collagen diseases".

Discussion.—DR. CHARLES L. STEINBERG (*Rochester, N.Y.*): The electrocardiogram showed that this patient had left axis deviation. In the monumental work that Soma Weiss did on systemic scleroderma just before his death (Weiss, 1943), practically all his cases had abnormal electrocardiograms: two had partial heart block and two had left ventricular preponderance. These patients had marked fibrotic changes in the lungs causing also right cardiac hypertrophy.

I should like to ask Dr. Bayles whether this tracing was characteristic of his other cases or whether it happened to be true because this patient probably also had coronary disease. Dr. Bayles should be congratulated for again emphasizing the systemic nature of this disease.

DR. IRVING LEINWAND (*New York, N.Y.*): We had the opportunity of studying about 200 patients with scleroderma, and autopsied about eleven. We found everything that Dr. Bayles has reported, but one additional finding was the presence of pronounced arteritis. I never saw a patient who died of scleroderma without an arterial lesion, and it is our experience that most patients before they died developed a hypertension, usually associated with some renal lesion. Were the kidneys in the nine patients who died examined very closely?

DR. ANTOINETTE POPOVICI (*Washington, D.C.*): How many patients had high blood pressure and how many had slight heart failure in these eighteen cases of hypertension of the lung? Only one had cardiac hypertension, and I should like to ask what kind of relationship this had with the hypertension in the lung.

CHAIRMAN: I should like to ask Dr. Bayles if he would say a further word about the effect of sympathectomy. He mentioned it briefly.

DR. BAYLES: First, in reply to Dr. Steinberg's question, I happen to have here the summary of the electrocardiographic findings, and, despite the pulmonary lesion which is so common, I have only one patient who showed right axis deviation. Of course, we knew of Dr. Weiss's patients, ours were seen later than his. I am not an electrocardiologist, but I think that perhaps the triangular enlargement of the heart accounts for the fact that we did not get this preponderance to the right in the electrocardiogram.

As to the question on renal lesions, two patients have developed severe hypertension. Albuminuria is certainly a common manifestation, but none of our patients died a renal death except perhaps the one with malignant hypertension, who died of cerebral haemorrhage and had some uraemia.

There is no question but that arterial vascular lesions occur in this disease, and Pagel in London and many other people have described the diffuse vasculitis which is often seen. The kidney is, of course, not excepted in this process. Only two patients, however, developed severe hypertension.

As to sympathectomy, I know there have been favourable reports, and I would say this about it: we have had about eight patients who had very thorough sympathectomies, and they got relief from the point of view of the Raynaud's syndrome. I did not mention that twelve out of our fifteen patients had Raynaud's syndrome. Unfortunately, the improvement is not usually permanent because the sympathetic nervous system is able to re-supply various areas of the body. I am not much impressed by the effects of sympathectomy in scleroderma except insofar as it affects the Raynaud's syndrome.

Recent Contributions to the Understanding of the Metabolic Defect in Gout. By DEWITT STETTEN, JR., *New York, N.Y.* (by invitation).

Studies in normal men carried out with the aid of isotopic (N^{15}) uric acid have revealed that there exists a miscible pool of uric acid in the body amounting, on the average, to about 1·1 g. This uric acid is turning over at a rate such that ½ to ¾ of the pool is replaced each day by newly-formed uric acid. About 80 per cent. of the uric acid disposed of each day is eliminated as uric acid in the urine. The major portion of the remainder is catabolized, its nitrogen appearing as urea and ammonia in the urine.

In the gouty subject the magnitude of the miscible pool of uric acid is increased. Values as high as 30 g. have been observed. It has been calculated that all of this miscible uric acid could not exist in a saturated solution in the total water of the body and it has been shown that at least the peripheral layers of tophi contain uric acid which contributes to the miscible pool, presumably as a consequence of continuous resolution and precipitation of urates. The prolonged administration of uricosuric drugs results in a shrinkage of the miscible pool of uric acid in gout.

In some but not all gouty patients the rate of synthesis of uric acid from dietary glycine was found to be strikingly enhanced. This finding was correlated with the

basal level of urinary uric acid excretion. Both in the normal and in the gouty individual a positive correlation between rate of uric acid synthesis and level of protein in the diet was demonstrated.

Discussion.—DR. L. MAXWELL LOCKIE (*Buffalo, N.Y.*): Dr. Talbott, Dr. Norcross, and I have been interested in this particular problem for the last 3 or 4 years. Our work in Buffalo is in agreement with that of Dr. Stetten.

One matter of interest is the possible action of colchicine, it is highly suggestive that colchicine has an effect similar in nature to that of ACTH.

We are also working on Butazolidin and Benemid and our results will be available for the International Congress at Geneva in September.

DR. GEORGE G. HAYDU (*New York, N.Y.*): I should like to ask about the last phase of the shunt. Would it be possible that, instead of this shunt from dietary glycine nitrate uricase in gouty subjects, there may perhaps be a regular lengthening of the adenine polyphosphates followed by a much faster destruction of the nucleic acid.

DR. STETTEN: In regard to the studies with colchicine, our single experiment was conducted quite differently from those published from the Buffalo laboratory, in that ours was an acute experiment. The patient was not fully colchinized; we gave colchicine on 2 days, whereas it is my recollection that it was used in the Buffalo experiments over a considerably longer period. This perhaps accounts for our failure to detect any effect of colchicine as we studied it.

The shunt which is postulated appears to be required by the fact that after giving glycine N^{15} to these selected gouty patients, the isotope abundance rises rapidly and falls rapidly. This indicates that at least a portion of the uric acid is being formed from small reservoirs of precursors that are turning over rapidly. In certain situations, hyperuricaemia undoubtedly results from the more rapid turnover of portions of nucleic acid. We recently studied a patient with polycythaemia, and in this situation it is altogether probable that the hyperuricaemia arose from the rapid turnover of the nucleic acids which normally comprise the nuclei of red cells.

However, it is my impression that in most gouty subjects no cytological evidence is forthcoming to suggest a more rapid turnover of nucleic acids in any particular tissue. If an isotopic material such as ammonia is fed to the pigeon one finds higher concentrations of N^{15} in the urinary uric acid than one does in any sample of adenine that has thus far been studied. From this it may be concluded that, in the bird, nucleic acid adenine and guanidine are not obligatory intermediates in the formation of the uric acid, which the bird forms at a very much higher rate than the mammal.

A thought that has been knocking around our laboratory is that the metabolic defect in gout may perhaps be related to this normal pathway in the bird in a vestigial sense, and that the gouty mammal has a uricotelic metabolism without the advantage of the bird's kidneys, which can concentrate uric acid far more effectively than those of the mammal.

Haemagglutination Test for Rheumatoid Arthritis—A Clinical Analysis. By ABRAHAM S. JACOBSON, WILLIAM H. KAMMERER, MAXWELL H. KOLODNY, and GEORGE HELLER, *New York, N.Y.*

The results obtained with a haemagglutination test for rheumatoid arthritis applied to approximately 1,000 individuals, have been analysed. 1,541 serological determinations were performed and 165 joint fluids (from 42 patients) were tested. All sera and joint fluids tested were rendered free of sheep erythrocyte agglutinins by absorption. A 0·5 per cent. suspension of sheep erythrocytes was sensitized with a 1/20 dilution of the basic agglutinin titre of any lot of sheep erythrocyte antiserum. The test sera and joint fluids were diluted in saline and agglutination titres against the sensitized sheep erythrocytes determined. A second agglutination titre was similarly determined, diluting the test sera and joint fluids in 5 per cent. sheep serum instead of saline. If the titre obtained in sheep serum diluent was four-fold, or more than that obtained in saline, the result was considered positive.

Of 261 cases of definite active peripheral rheumatoid arthritis, 192 (74 per cent.) were serologically positive by this technique in one or more of multiple determinations. Of thirty cases of active peripheral rheumatoid arthritis in which joint fluids were thus tested, 23 (77 per cent.) were positive. Seven false positives were obtained: three in patients with diffuse collagen disease, two rheumatoid spondylitis with no evidence of active peripheral rheumatoid arthritis, one cirrhosis, and one "fibrositis".

The titres determined were compared with the clinical course of the disease, sex, duration, and severity.

Discussion.—DR. HOWARD C. COGGESHALL (*Dallas, Texas*): Our work corresponds very closely to these findings. We have recently reviewed our work with some eighteen reports published since the test became popularized. Out of a total of 6,500 individuals tested, 1,800 had rheumatoid arthritis: 64 per cent. of the group suffering from rheumatoid arthritis showed significant agglutination, miscellaneous disease accounted for 4 per cent. of the positive tests, and 0·6 per cent. of normal people were found to have a positive test.

In our experience, we found positive tests in a few patients with scleroderma and serum sickness. I think the data presented are very interesting in that some of the false positives reported were in patients with skin disease. It is possible that the agglutinating factor is increased in the presence of acute allergic reactions of the skin.

We have also reviewed the data on 63 patients with rheumatoid arthritis who had repeated tests made during a period of 29 months. The serum had been stored in a frozen state. Our findings showed very little change in the original titres. Of 63 patients, 61 showed positive titres on repeated tests; six of these showed a four-fold decrease in titre, nine showed an increase, and four showed a negative titre even though they had progressive disease.

One does see patients with severe disease who will remain with negative titres.

Our data differ from those reported, in that of our 177 patients (61 males and 116 females), the females showed higher titres.

It seems that the titres are always higher after the disease has been present for more than a year, and where the disease is more advanced. I think this agglutination factor is remarkably stable, will remain unchanged after being frozen for periods up to $2\frac{1}{2}$ years. It may have some significance of an aetiological nature, but is of little help in diagnosis.

DR. R. W. LAMONT-HAVERS (*New York, N.Y.*): The need to elucidate more clearly the significance of the

sensitized sheep cell test is great, and it is hoped that this new technique may lead to a better understanding of the fundamental problems in this reaction.

We have been studying the inter-relationships of the two agglutination reactions of rheumatoid serum, namely, that against sensitized sheep cells and that against Group A haemolytic streptococci. We found that we were able to obtain a relatively large precipitate from rheumatoid sera with highly sensitized sheep cell titre when this serum was diluted 1 to 20 with water. With normal serum, only a very slight precipitate or none was obtained.

The factor responsible for the sensitized sheep cell reaction was found in this precipitate which is in the γ globulin fraction by paper electrophoresis.

Of further interest is the fact that the streptococcal agglutination reaction requires both the precipitate and the supernatant fractions. While the precipitate factor is specific for rheumatoid serum, the supernatant factor may be replaced by that from normal adult human serum, but not by the serum from most children under 8 months, or from several animal species. The supernatant factor is chiefly found in the globulin precipitated by dialysis against distilled water.

The supernatant factor must be absorbed by the streptococci before the factor in the precipitate can agglutinate streptococci. In some sera, this supernatant fraction may be the limiting factor of the streptococcal agglutination reaction. While it is possible that this factor is an antibody, it may not be specific for Group A streptococci, but may rather be a non-specific response to stimuli of Gram-positive organisms. This still has to be determined.

There would thus seem to be a similarity between the streptococcal agglutination reaction and the sensitized sheep cell agglutination reaction. Reciprocal absorption experiments, however, would indicate that the factor in the precipitate responsible for the sensitized sheep cell reaction and streptococcal agglutination reaction are not identical but possibly closely related γ globulins. Whether these are abnormal globulins or represent an increase of globulins normally present, is not yet known.

DR. THEODORE B. BAYLES (*Boston, Mass.*): This is work that was done in our laboratory by Dr. John H. Vaughan, who is here, and Mr. Andrew Armato, who is our research technician.

Dr. Vaughan is publishing a report that plasma Fraction 2 (Cohn's Fraction 2), which is 95 per cent. γ globulin, does not contain this agglutinin, but Fraction 3, by this technique of fractionation and then iodinization, does show the responsible agglutinin. Fraction 3 is a composite of β and γ globulins.

I think it is important for everybody who works with these things to realize the heterogeneous nature of γ globulins. We reported last year our inability to find any specificity of γ globulins for connective tissue, or joint tissues, by this technique of fractionation and iodinization.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): We have been studying the nature of the haemagglutination factor in the sera of patients with rheumatoid arthritis since last autumn, using the Heller-Jacobson technique. Dr. Saroff and Dr. R. R. Williams, Jr., of our Institute, are now attempting to define the chemical nature of this factor. Thus far, the results show, in a preliminary way, that the factor is apparently a macromolecule greater than 15,000 or attached to a macromolecule which is not dialysable to cellophane. It is stable from *p*H 3 to 11, and at a temperature of 37° C. it is stable in 30 per cent. alcohol. We believe that this factor is not a complement.

DR. RUSSELL L. CECIL (*New York, N.Y.*): I was interested in what Dr. Coggeshall said about the value of these tests in the differential diagnosis of doubtful cases of arthritis. I think Dr. Coggeshall is a little too pessimistic, and should like to know Dr. Jacobson's opinion.

In my own experience I have found, in looking at joints, that this test is often of considerable value, especially since we find that 40 or 45 per cent. of rheumatoid cases will give a positive reaction during the first 6 or 12 months of the disease. I believe that the test will have an important place in differential diagnosis.

Another interesting point is the long persistence of these agglutinins in the blood after a patient has gone into remission, which rather indicates what Ragan and others have contended: that rheumatoid arthritis is essentially an incurable disease.

DR. CHARLES M. PLOTZ (*Brooklyn, N.Y.*): We have been interested in the Heller-Jacobson technique of using animal and human serum as a diluent rather than saline. At Mount Sinai, we have been using as a diluent, pooled human Red Cross plasma, which has been inactivated, tested, and shown to be negative. We find this gives a 2- to 4-fold increase in positives in the differential sheep cell reaction. Unfortunately, however, it very often gives a 2- to 4-fold increase in negatives, and we have been unable to find that the use of plasma as a diluent has been of any help in increasing the number of positives in this test.

DR. J. J. R. DUTHIE (*Edinburgh, Scotland*): I should like to ask if they found any difference in titre in joint fluid and serum in cases where both tests are being done.

DR. HELLER: In reply to the last question, our results have shown that a majority of the sera exhibit titres not significantly different from the values obtained from knee fluids.

For the purpose of obtaining a more definite chemical characterization of the plasma component which is responsible for the specific haemagglutination of sensitized sheep erythrocytes, we have tested, by our procedure, the various plasma fractions prepared by the cold-ethanol methods of E. J. Cohn and others. In this study, which was carried out in collaboration with Dr. I. H. Lepow of the Institute of Pathology, Western Reserve University, Cleveland, Ohio, we found that the haemagglutination factor associated with active peripheral rheumatoid arthritis is in Plasma Fraction III-1. Our procedure was especially useful in identifying this fraction as responsible for the agglutination reaction, since other haemagglutination tests have no means of differentiating specific from non-specific reactions.

As Dr. Jacobson indicated, our procedure depends upon the testing of serum aliquots diluted concurrently in saline and in sheep serum to which sensitized sheep erythrocytes are added. When a serum from a case of active peripheral rheumatoid arthritis is assayed, the resulting positive reaction is indicated by the fact that the titre in sheep serum diluent is 4-fold or more greater than the titre of the serum aliquot diluted in saline. When sera from non-rheumatoid individuals are tested, the resulting agglutination titres are equal in both diluents and the reaction is considered negative. The latter type of reaction is due to the non-specific conglutinin property of the serum common to man and other animals. With other haemagglutination procedures, no such differentiation is apparent. We demonstrated with our procedure, however,

that Fraction III-1 possessed both the agglutination property associated with rheumatoid arthritis and the non-specific conglutinin property. When this Fraction was obtained from individuals with active peripheral rheumatoid arthritis, it exhibited a positive agglutination reaction. When it was obtained from non-rheumatoid individuals it exhibited a negative reaction.

DR. ANTOINETTE POPOVICI (*Washington, D.C.*): I should like to know how many of these tests were done in rheumatic fever as compared to polyarthritis.

DR. JACOBSON: We examined about seventy such patients, and they were all negative by this test.

With regard to Dr. Cecil's comment, we have been fortunate enough to have a number of proven gout cases, also with rheumatoid arthritis proven by microscopic examinations of peripheral nodules, who were positive by the test, and I rather agree with Dr. Cecil that there are instances where diagnostically the test is of great help, although in general I am quite sure that our clinical acumen is as good as the test.

Length of Life and Cause of Death in Rheumatoid Arthritis. By SIDNEY COBB, FLORENCE ANDERSON, and WALTER BAUER, *Boston, Mass.*

Short life tables have been based on 583 patients hospitalized at the Massachusetts General Hospital with rheumatoid arthritis and subsequently followed for an average of 9·6 years. During the period of study there were 137 deaths, which have been analysed by cause.

Though rheumatoid arthritis is seldom given as a cause of death, the group of hospitalized patients here reported was found to have a higher mortality than would be expected had the group been drawn from the general population. This was found to be due to the fact that younger people, particularly males, succumbed more rapidly than expected; patients over 50 years of age were not apt to have their longevity altered.

The causes of death in rheumatoid arthritis differ from those in the population at large. Notable for their frequency are valvular heart disease, infections of all sorts, renal disease, and pulmonary embolism. Notable for their absence or infrequency are accidental deaths, hypertensive heart disease, and myocardial infarction.

These conclusions are sufficiently interesting to warrant further study in larger series, so that the life tables can be broken down into smaller age groups and by marital status, and more significant conclusions can be drawn about differences in the causes of death between arthritics and the general population.

Discussion.—DR. J. H. KELLGREN (*Manchester, England*): This idea that rheumatoid arthritis is never lethal has always seemed to me a peculiar one, because in the British Registrar-General's record of deaths, rheumatoid arthritis as a main case is certified in quite a significant number of individuals. In fact, the mortality from rheumatoid arthritis so certified is not much less than that from rheumatic heart disease, which we all recognize to be a prominent killer. I think that the rheumatoid patient may well deteriorate, as we have seen from these figures, in a much more striking way than has previously been recognized.

DR. COBB: In answer to Dr. Kellgren, I should like to mention that no single one of these 130 patients was recorded as having died of rheumatoid arthritis. I think it is perhaps less common in the U.S.A. to give that diagnosis on the death certificate than it is in England. Examination of our vital statistics shows that very many fewer deaths are recorded as due to that cause in the U.S.A. than in Great Britain. This is probably due to a difference in the customs of medical reporting in the two countries.

Polyarteritis in Rheumatoid Arthritis. By WILLIAM D. ROBINSON, A. JAMES FRENCH (by invitation), and IVAN F. DUFF, *Ann Arbor, Mich.*

Four patients with well-documented rheumatoid arthritis have been observed to develop severe neurological disturbances (primarily peripheral neuritis), associated with various other unusual clinical manifestations which were eventually correlated with severe diffuse arterial pathology.

In two patients there was clinical and pathological evidence of severe cardiac involvement and coronary arteritis, which appeared to be the immediate cause of death: in one of these, the unusual clinical manifestations first appeared during the sixth to eighth month of ACTH treatment for rheumatoid arthritis; in the second they appeared when cortisone therapy was discontinued gradually after 10 months because of localized osteoporosis and compression fracture of lumbar vertebrae. In the third patient, they appeared after ACTH was discontinued because of a perforated gastric ulcer, and it was impossible to control severe constitutional and neuritic manifestations until small doses of ACTH were resumed 4 months later.

The fourth patient, in whom death was due to occlusion of a cerebral artery, was observed before ACTH and cortisone became available.

Careful study of the pathological findings in these four cases has led to the impression that the arterial lesions differ qualitatively from those of classical periarteritis nodosa, particularly with respect to their distribution, lack of regional involvement, and usual absence of necrotizing arteritis. The lesions are qualitatively similar in all four cases, but are definitely more active in the three who received hormone therapy than in the one who did not. They appear to be of the type which have been described previously as features of the systemic pathology of rheumatoid arthritis. Unless similar observations have been recorded by others, no definite conclusion with respect to the role of hormonal therapy in the development of these lesions and their clinical manifestations seems justified.

Diffuse Systemic Rheumatoid Disease. By M. A. OGRYZLO, *Toronto, Canada.*

Although rheumatoid arthritis may vary widely in its clinical course and in the severity of its manifestations, it is rarely cited as the cause of death. In the past 7 years a number of patients have been observed to exhibit a severe and sometimes fulminating form of rheumatoid disease, characterized by a deforming polyarthritis and

associated with involvement of other viscera. Eight such patients are reviewed, of whom six have succumbed to the disease. The cases illustrate what may rarely constitute the terminal course of events in patients with otherwise classical rheumatoid arthritis. Pathological studies were made in four patients who came to autopsy.

The duration of the joint manifestations, which comprised a deforming polyarthritis in all instances, varied from 2-38 years. Fever, weight loss, secondary anaemia, leukopenia, elevated sedimentation rate, and increased serum globulins, with subcutaneous nodule formation, and enlargement of the lymph nodes, liver, and spleen, were common accompaniments of the disease. Involvement of other viscera included pulmonary infiltrations, frank consolidations, pulmonary fibrosis or bronchiectasis, pleurisy with or without effusion, cardiac decompensation with E.C.G. changes, pericarditis with or without effusion, renal manifestations with albuminuria, red cells, and casts, and diffuse muscular wasting. Cutaneous lesions were not a feature of the syndrome, although a severe exfoliative dermatitis developed in two patients who received gold.* The lupus erythematosus cell reaction was positive in four patients.

The pathological changes were strikingly similar in the patients studied at autopsy. These included fibrinous pericarditis, fibrinous pleurisy, areas of diffuse and perivascular myocardial fibrosis or round cell infiltration, varying degrees of interstitial pneumonia or pulmonary fibrosis, vascular changes including periadventitial fibrosis and intimal thickening or a necrotizing arteritis, diffuse and focal myositis, thickening of the glomerular basement membranes, and rheumatoid nodules. Small sarcoid lesions were present in two instances and amyloid deposits in one.

Discussion.—DR. HOWARD J. WEINBERGER (*Los Angeles, Calif.*): These reports emphasize again the systemic nature of rheumatoid arthritis and the difficulties encountered in distinguishing it from certain other connective tissue diseases. We have observed unusual clinical and histopathological manifestations of vasculitis in fifteen patients with rheumatoid arthritis.

Nine of these patients had received ACTH or cortisone for periods varying from 2 weeks to 2 years; five of them developed clinical manifestations of arteritis while on it, and four after it was stopped. The duration of the rheumatoid arthritis before the appearance of the arteritis was from 4 months to 20 years. The severity was Stage II to IV. Thirteen of the fifteen patients showed destructive joint alterations on *x*-ray examination; rheumatoid subcutaneous nodules were present in seven patients, the majority of which were biopsied; synovial membrane biopsies in three patients were consistent with rheumatoid arthritis. The manifestations of arteritis were recognized clinically in only ten out of the fifteen, eight of whom were in the cortisone group. This may represent only an increased interest in the cortisone group, inasmuch as in retrospect all but one of the fifteen patients had had clinical manifestations. These included purpura, spontaneous necrosis and ulceration of the skin, delayed wound healing, breakdown of old wounds, digital gangrene, peripheral neuritis, and in one hemiplegia. In three patients, death apparently resulted from mesenteric artery thrombosis and gangrene of the bowel. Four patients had advanced renal disease, one showing the typical telescopic urine of periarteritis nodosa. Three patients had advanced cardiovascular involvement.

A *post-mortem* examination was made in all the nine patients who died, five of whom came from the non-treated group, and four from the cortisone-treated group. It is interesting that muscle biopsy in two patients was negative for arteritis before death, and that in two other patients who died, arteritis had been demonstrated by muscle biopsy 4 and 3 years before death.

In the surviving patients, the histological proof of arteritis was obtained by skin biopsy in two, and by muscle biopsy in four. There was a good deal of variation in the appearance of the lesions of arteritis, both in the same patient and between patients, and no consistent difference was recognized between the treated and the untreated group.

At times some of these lesions were indistinguishable from the arteritis lesion of periarteritis nodosa. We also observed lesions in the walls of larger arteries that resembled very much the rheumatoid subcutaneous nodule. We also saw the lesions of arteritis in blood vessels related to the rheumatoid subcutaneous nodules.

This we believe adds support to the concept that arteritis may form part of the basic pathological process of rheumatoid arthritis.

Eight of the nine patients who died, apparently did so as a consequence of or secondary to the arteritis. The clinical manifestations of arteritis were in remission in two of the surviving patients, and progressive in three, and the course of the arteritis was unknown in one, but the arthritis was apparently progressive in all of them. We were unable to draw any conclusions regarding the relationship of cortisone to these lesions, but it is apparent from our experience that in some patients cortisone did not prevent the development of these lesions, and certainly did not prevent the fatal complications.

We had previously been impressed by the relative specificity of the L.E. cell test in lupus erythematosus. In five of our patients in whom the tests were done, negative results were obtained. We do not know how to interpret Dr. Ogryzlo's report of positive lupus erythematosus phenomenon in rheumatoid arthritis, but we are inclined to discount the specificity of the test in his cases.

DR. FELIX E. DEMARTINI (*New York, N.Y.*): The systemic nature of rheumatoid arthritis has become more evident during the past ten years. The histological lesions of the diffuse involvement of the nerves, muscles, and vessels, in addition to synovial disease, have been widely reported. Clinically, however, extra-articular manifestations have been infrequently recorded, and when visceral symptoms have presented themselves in patients with rheumatoid arthritis, they have been usually ascribed to an unrelated process.

This morning, these two reports described diffusely disseminated rheumatoid arthritis. In the past 2 years we have observed a diffusely malignant disseminated disease, the cause of death being directly related to the rheumatoid process in the heart. The case histories of Dr. Robinson resemble those we have observed.

A large necrotic nodule was seen histologically in the mitral valve in a 45-year-old female with rheumatoid arthritis of 15 years' duration. There was no past history of rheumatic fever, and no cardiac abnormalities were present 8 months before death. She was treated with cortisone for approximately 2 years. All phases of this

* Both responded to BAL.

large necrotic nodule were seen, and there were many small arterial lesions in its periphery, in the epicardial, myocardial, and endocardial surfaces; no Aschoff bodies were seen in multiple sections of the myocardium. In many other sections where no gross lesions were seen, histological evidence of a diffuse arteritis was present.

Scarred valves in patients with rheumatoid arthritis do not necessarily represent previous rheumatic fever, but may represent the rheumatoid process itself, as our two cases seem to indicate.

We have recently examined the *post-mortem* findings in patients with rheumatoid arthritis since 1930 at the Presbyterian Hospital. In a total of fifteen cases death was not directly attributed to rheumatoid arthritis *per se*.

One can only speculate as to the influence of cortisone and ACTH on the natural history of rheumatoid arthritis. We have recently reviewed our patients on long-term cortisone-ACTH therapy, screening with lupus erythematosus cell preparations, and have not as yet had a positive test.

DR. MORRIS ZIFF (*New York, N.Y.*): Dr. Leon Sokoloff of our study group has recently examined specimens of gastrocnemius muscle obtained by biopsy from five patients of a group receiving long-term cortisone therapy at Bellevue Hospital, under the direction of Dr. Bunim. An additional muscle sample was obtained at autopsy. None of these patients had the severe periarteritis-like disease reported by Drs Robinson and Ogryzlo. The cortisone dosage was between 50 and 100 mg. daily, and the duration of treatment between 3 and 29 months. Five of the biopsies showed no remarkable changes. In one patient, who had received between 67 and 100 mg. cortisone daily for 15 months, examination of the muscle showed evidence of intimal fibrosis of isolated small arteries. An earlier biopsy of a subcutaneous nodule obtained from this patient 7 months after the initiation of cortisone therapy showed evidence of active arteritis of the subcutaneous nodule, and intimal fibrosis and vascularization in the attached skin. This incidence of one arteritic lesion in six patients on cortisone 16 per cent., though in a small sample may not turn out to be appreciably greater in a larger series than the incidence of approximately 10 per cent. in untreated cases of rheumatoid arthritis recorded by Sokoloff, Wilens, and Bunim, who noted the lesion six times in 67 muscle biopsies in patients who had not received cortisone.

DR. CHARLES H. SLOCUMB (*Rochester, Minn.*): Hypercortisonism or a hyperadrenal state induced by administration of cortisone or corticotropin (ACTH) for a variable period does something in patients with rheumatoid arthritis not observed in patients with other diseases, except possibly lupus erythematosus. One reaction was described a year ago: it occurs in some patients who have hypercortisonism or who are in a hyperadrenal state. It is characterized by fatigability with emotional instability, and muscular and articular aching when the patient becomes physically or mentally fatigued, alternating with a feeling of restless energy and impatience after periods of rest or soon after a dose of the hormone. The other reaction occurs when the dosage of the hormone is decreased; when it is stopped abruptly all patients have withdrawal reactions, when it is reduced slowly, patients may show any of four types of reactions:

they may have a gradual release from the signs and symptoms of hypercortisonism with progressive improvement until the dose is from 20 to 30 mg. cortisone daily and then they may have difficulty with further reductions, or they may react with panmesenchymal panangiitis simulating a rheumatoid flare, or with lupus erythematosus, or with periarteritis nodosum.

The panmesenchymal reaction is potentially serious unless the reduction in dosage is gradual. My colleagues and I have observed death from a cerebral accident in a patient who reacted with periarteritis nodosum even on gradual reduction of dosage.

Of fifteen patients whose blood contained lupus erythematosus cells, one has now had a negative test for lupus erythematosus cells.

Of three patients with microscopic evidence of a periarteritis nodosum-like reaction, one improved markedly after gradual withdrawal of cortisone.

The severity of the panmesenchymal reaction during withdrawal of cortisone or corticotropin is no indication of the amount of rheumatoid arthritis which will still be present when the patient has recovered from the hypercortisonism and panmesenchymal state.

DR. RICHARD T. SMITH (*Philadelphia, Pa.*): We had a patient who died 2 weeks ago, who had had rheumatoid arthritis for approximately 2 years. One year ago she was started on cortisone, and the dosage had been reduced to 37·5 mg. according to the directions of her physician. When we saw her about 8 weeks ago, we learned that on her own she had been taking 125 mg. a day for some months. She still had evidence of activity of rheumatoid but not severely so. We decreased the cortisone slowly and started her on gold, of which she received four injections, or a total of 70 mg. She was admitted to the hospital 4 weeks after discontinuing the cortisone with peripheral neuritis involving all four extremities, but more severe in the upper extremities.

The question of cause came up. Immediately the gold was blamed, but no other cause was brought forward. A neurologist confirmed the diagnosis of peripheral neuritis. We found her haemoglobin level was 5 g., and gave a blood transfusion. About a year before, in another hospital, she had also had a low haemoglobin and had received a blood transfusion, which corrected it.

During her stay in hospital there was no improvement in the peripheral neuritis. She received 40 mg. ACTH daily in the hospital, and while receiving a third blood transfusion developed a cerebral accident and died within 6 hours.

The preliminary autopsy report indicated that she not only had demyelinization of the peripheral nerves but also degenerative changes of nerve tracts in the spinal cord. We have not been able to determine the background of all these findings, but a complete autopsy report is being prepared, and we think that this spinal lesion should also be considered among those mentioned this morning.

DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): I agree with the facts presented in these papers, but some years ago, in the days of B.C. (before Cortisone), we reported some fifteen cases of this kind that went insidiously from characteristic chronic rheumatoid arthritis to what we then called diffuse collagen disease, not diffuse rheumatoid disease. Some were characteristic of lupus, some of periarteritis nodosa, and some in between.

I am not convinced that these are cases of uncomplicated rheumatoid arthritis, nor that they belong entirely to the picture of rheumatoid arthritis. We have all seen these patients, and we are continuing to see them in the post-cortisone era, just as we did before cortisone. I, like Dr. Robinson, have a feeling that those which now occur are more fulminating than those which we saw before cortisone, but I do not think we can yet be certain whether the cortisone is responsible. I am sure it is much

too soon to substitute the term "diffuse rheumatoid disease" for "diffuse collagen disease".

DR. CHARLES RAGAN (*New York, N.Y.*): I should like to agree with Dr. Holbrook, but there is one thing that I think important. If we take a rheumatoid nodule out of the specificity of this disease, we end with somewhat of a hodge-podge. I should like to ask Dr. Ogryzlo how many of his patients had typical rheumatoid nodules or just a type of tissue reaction.

DR. EUGENE F. TRAUT (*Chicago, Ill.*): I think most of us are convinced of the systemic nature of rheumatoid arthritis. Dr. Robinson and Dr. Ogryzlo are to be congratulated for re-emphasizing the widespread nature of the tissue changes. We are reminded of the early work of Freund and others (1945).† In biopsies of muscles from patients with rheumatoid arthritis they found many of the changes first reported by Curtis and Pollard (1940).‡ The report of our own more recent studies of muscles was given last year.* We found many of the arterial lesions described by Sokoloff, Wilens, and Bunim (1951),§ but not the nerve lesions emphasized by Freund.

We found cellular infiltrations especially marked in a case treated with cortisone, the infiltration in places amounting to a lymphorrhoea. A group of ambulatory patients with rheumatoid arthritis from the arthritis clinic of Cook County Hospital did not show "L.E. cells".

DR. IRVING LEINWAND (*New York, N.Y.*): I should like to carry Dr. Holbrook's point a little further; rheumatoid arthritis is frequently diagnosed in early lupus, early scleroderma, and early dermatomyositis. Many of the cases reported to-day may easily fall into one of those three categories.

The diagnosis of dermatomyositis is very rarely made in the U.S.A., but appears frequently in the British literature. It could be considered identical with scleroderma if the skin lesion were eliminated, and it could easily fit several of the cases that have been presented. If we enlarge the category of rheumatoid arthritis, we shall have to include disseminated lupus erythematosus, scleroderma, and possibly periarteritis nodosa.

DR. OTTO STEINBROCKER (*New York, N.Y.*): It is hardly necessary to add that this is one of the very difficult areas of diagnosis and treatment. We have followed it for a long time by the antediluvian method of clinical observation, with a little technical assistance, and have seen what we thought were characteristic collagen disorders developing in rheumatoid arthritis.

The information which is now emerging may cause confusion in the minds of many members, but will undoubtedly clarify the situation in time. The two papers we have heard on this subject are extremely helpful and illuminating. It seems, from what has been said and from what is known, that patients with rheumatoid arthritis may develop any of these specific collagen entities, and that patients with any of these particular entities may also develop rheumatoid-like features or possibly rheumatoid disease. For the sake of prognosis, and sound treatment, until the situation has been made clearer with further information of the kind we have received to-day, it is important to bear these distinctions in mind, complicated as they sound.

This information must be carefully collected until all the facts are known and we have a clear-cut understanding whether rheumatoid arthritis is a collagen disease clinically (so far it certainly has distinct characteristics), and whether in such cases as were shown here we see the merging of these various diseases. The experience with the small number of cases shown should not influence the clinical management of these conditions until we know more about them.

DR. ROBINSON: With respect to the differentiation between collagen disease and rheumatoid arthritis, I should like to emphasize that the three patients who received hormone therapy were observed for long periods to have all the characteristics of rheumatoid arthritis, and we had no reason to question that diagnosis until the development of the bizarre clinical picture which we have described.

For the sake of completeness, I should like to state that only one of the three was tested for lupus erythematosus cells, and he was found not to have them. All four patients showed marked abnormalities in the electrophoretic pattern of plasma proteins, and one patient with severe lesions had cold-precipitable globulins in the plasma.

DR. OGRYZLO: The question whether these cases might be regarded as atypical lupus erythematosus with arthritis was considered. To some extent this depends on one's point of view: one might regard the demonstration of the lupus erythematosus phenomenon as in itself diagnostic of this disease, especially if this is regarded as a specific test. I personally do not regard it as specific, although I would agree that it may be indicative of a particular type of tissue reaction, specific tissue injury, or hypersensitive state. In addition to the patients reported to-day, we have demonstrated the lupus erythematosus cell reaction in one patient with diffuse scleroderma, and in one with Marie-Strümpell spondylitis not associated with peripheral joint involvement.

To label these cases as lupus erythematosus would entail conceding a number of points: firstly, that the lupus erythematosus cell reaction is specific (others have described this reaction in a number of different diseases which I shall not attempt to list here); secondly, that disseminated lupus can manifest itself as a chronic deforming and destructive arthritis, for periods as long as 38 years (if such were the case, it would mean that the diagnosis could not have been made for this length of time or possibly not at all in those cases in whom the lupus erythematosus cell reaction was not positive); thirdly, that typical juxta-articular rheumatoid nodules may occur in lupus erythematosus (a phenomenon which we have never observed in classical lupus erythematosus). One of our patients with rheumatoid arthritis and juxta-articular nodules had a strongly positive lupus erythematosus cell reaction.

Another interpretation is that these patients suffered from a combination of rheumatoid arthritis and lupus erythematosus. I see no reason for such a compromise; I feel that they are best regarded as suffering from one disease throughout, differing only in severity and in type of manifestation. Several observations support this view: the typical skin rash of lupus erythematosus, valvular lesions of the Libman-Sacks type, and hypertension were all absent, whereas the pulmonary fibrosis and bronchiectasis which were present have not been described in lupus erythematosus.

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* Traut, E. F., and Campione, K. M. (1952). *Arch. intern. Med.*, **89**, 724.

† Freund, H. A. (1945). *Science*, **101**, 202.

‡ Curtis, A. C., and Pollard, H. M. (1940). *Ann. intern. Med.*, **13**, 2265.

§ Sokoloff, L., Wilens, S. L., and Bunim, J. J. (1951). *Amer. J. Path.*, **27**, 157.

Comparative Effects of Hydrocortisone Free Alcohol, Hydrocortisone Acetate, and Cortisone Acetate in Rheumatoid Arthritis. By L. E. WARD, P. S. HENCH, C. H. SLOCUMB, and H. F. POLLEY, *Rochester, Minn.*

Hydrocortisone or one of its esters, administered orally or intramuscularly to 31 rheumatoid patients and to one patient with psoriatic arthritis, produced antirheumatic and other physiologic effects similar in nature to those resulting from administration of cortisone to the same patients.

Comparison of the antirheumatic potency of orally administered hydrocortisone free alcohol, hydrocortisone acetate, and cortisone acetate revealed that, milligram for milligram, hydrocortisone free alcohol was usually slightly more effective than cortisone acetate, and that hydrocortisone acetate was generally the least effective. The relative difference in antirheumatic potency of these three steroids varied considerably from patient to patient. A significant portion of the difference between cortisone acetate and hydrocortisone free alcohol could be accounted for by the fact that cortisone comprises by weight only 89 per cent. of a molecule of cortisone acetate, the remainder being the acetate radical.

When administered intramuscularly, hydrocortisone acetate and hydrocortisone cyclopentylpropionate appeared to be absorbed more slowly than cortisone acetate, as judged by clinical observations and by changes in erythrocyte sedimentation rate and urinary excretion of nitrogen, 17-ketosteroids, and corticosteroids.

The metabolic effects of hydrocortisone free alcohol, hydrocortisone acetate, and cortisone acetate were compared.

Discussion.—DR. MORTIMER E. EHRLICH (*New York, N.Y.*): At the Hospital for Joint Diseases we maintained eighteen patients on hydrocortisone free alcohol for periods of 12 weeks to 8 months. We did not attempt to differentiate the effectiveness of hydrocortisone from cortisone quantitatively, but we noted that smaller doses of the free alcohol were needed to achieve the results expected from cortisone.

With hydrocortisone, we graded the response of the patients thus:

Grade	I	1
Grade	II	5
Grade	III	9
Grade	IV	3

Of the eighteen patients, thirteen noted an effective relief from pain in spite of the failure of the drug to influence the grade of improvement.

Half of our patients developed side-effects and complications severe enough to require interruption and cessation of therapy. Four of the nine developed ankle oedema and gained weight in spite of low sodium intake; two developed hirsutism, and one a marked rise in blood pressure.

With maintenance dosage one of our patients in Grade I and one in Grade II who had maintained improvement for 5 months relapsed in spite of unchanged doses of hydrocortisone.

DR. PAUL J. BILKA (*Minneapolis, Minn.*): At the University of Minnesota we have been using hydrocortisone for the last 9 months. When we first obtained a supply of this material we attempted to repeat Boland's work by doing a rather rigid comparative study of cortisone acetate and hydrocortisone free alcohol, and we have some data on thirteen patients.

We took patients who had been on maintenance dosages of cortisone for rather long periods and substituted equivalent dosage, by weight, of hydrocortisone. Our results agree with those just presented by Dr. Ward. Of thirteen patients, three had about the same effect from equivalent doses of hydrocortisone free alcohol as they did from cortisone; eight had a 10 to 25 per cent. improvement; two improved from 25 to 50 per cent. and then required one quarter to one half less hydrocortisone to maintain a degree of improvement equivalent to that achieved by cortisone acetate. The ratio was closer to that presented by Dr. Ward, than to Boland's more optimistic one.

We also noted the similarity of side-effects in patients on hydrocortisone free alcohol with those in patients on cortisone acetate.

DR. WARD: We wish to emphasize particularly the factor of dosage in our study of long-term administration. We attempt to use doses low enough to avoid side-effects, and if side-effects develop, the dose is lowered until they disappear.

Comparison of Cortisone and Aspirin as Suppressive Agents in Early Cases of Rheumatoid Arthritis. By A. BRADFORD HILL and J. H. KELLGREN, *Manchester, England* (by invitation).

A small but strictly controlled therapeutic trial of cortisone and aspirin as suppressive agents in early cases of rheumatoid arthritis has been begun. Taking such early cases, uncomplicated by severe anatomical changes in the joints or by metabolic or endocrine disturbances resulting from prolonged illness, the object of the trial is

(*a*) to compare cortisone with aspirin as an agent for relieving the symptoms and improving the functional capacity of the patients,

(*b*) to compare the evolution of the rheumatoid process during prolonged therapy and to study the effects of withdrawal.

Only patients with a disease duration of 3 to 9 months were accepted. They were required to have a polyarthritis of rheumatoid type affecting at least four joints and a bilateral involvement of either hands or feet, ankles or wrists. Such cases admitted to each of six centres in Great Britain were initially divided by sex, age (16 and under, and 17-59 years), and disease duration (3-5 and 6-9 months). Within each of those sub-groups the treatment with cortisone or aspirin was randomly determined.

Treatment was given in 12-week courses, separated by one week without treatment. It was started with a short period of standard dosage followed by an individualized dosage aimed at restoring maximum functional efficiency without producing serious side-effects.

The results are being assessed in terms of clinical estimations of general functional capacity and of tenderness and range of movement of joints, the measurement of strength of grip, and two tests of dexterity, and

laboratory observations of the blood sedimentation rate and haemoglobin level.

There are fourteen juvenile cases (16 years or younger) of whom eight are on cortisone and six on aspirin. In the adult group (17-59 years) there are thirty patients on cortisone and 31 on aspirin. For the adult group it was possible to analyse the records relating to the first 12 weeks of treatment and the ensuing week of observation. Both treatment groups reveal, on the average, significant improvement in most of the measured features followed by a relapse in the week off treatment. The cortisone group reveals a rather greater improvement in the haemoglobin level and blood sedimentation rate, but in other respects the two treatment groups do not, at this first stage, differ materially.

Discussion.—DR. OTTO STEINBROCKER (*New York, N.Y.*): I am much interested in the various phases of this report, because I have been so closely tied up with the Committee on Therapeutic Criteria in the U.S.A. Any question I ask of a statistician of the eminence of Professor Hill is a calculated risk, but I do want to ask a few questions that puzzled me during this presentation.

First of all, it is difficult for me to understand why the criteria described were based largely on subjective phenomena. When we carefully considered this question in our own committee here, we ignored tenderness because it is to a great extent a subjective symptom. We also felt that personality factors were very important, and I should like to know whether those were taken into account.

But above all, I heard no mention of joint swelling, which is the only truly objective (visible as well as palpable) clinical evidence of rheumatoid involvement even in the early stages of disease, and I am very curious to know why it was omitted.

I am also wondering how, when, and where the matter of joint involvement fits into this evaluation. We have seen a number of patients who have good results but whose joints are still swollen. The tenderness is greatly relieved by the criteria Professor Hill has enumerated, yet I can see that by these standards you would fail to account for this very important feature. I should be interested to know how the clinical joint involvement in the group receiving aspirin differed from that in the group receiving cortisone.

I should also like to know how, even with this thoroughly randomized study by remote control, Professor Hill allows for the personal variations in the observers, who know they are participating in a grand therapeutic study.

Another question that arose as I listened was, what are the comparative constitutional effects on the patient? I think it is important to know what was the general response of the patient's appetite, weight, and so on. If this is to be regarded as a true evaluation of cortisone *versus* aspirin, there are many facts which should be supplied so that we may be thoroughly satisfied that our friends are aiming at a balanced estimate.

DR. J. J. R. DUTHIE (*Edinburgh, Scotland*): Before the discussion goes further, let me add something on the experience of another participating centre. We admitted to the trial some eighteen cases, and the centre register allocated ten to cortisone and eight to aspirin. (One of the cortisone cases was excluded, as has already been mentioned by Dr. Kellgren, because of the development of cardiac signs.) The average duration of treatment was 13 months for cortisone and 13·7 for aspirin.

We had to withdraw cortisone from two patients, and aspirin from two patients. The first cortisone patient was a girl aged 12, who, after 6 months on a maintenance dose of 100 mg. daily, developed marked mooning, striae, and oedema, and in whom *x*-ray examination showed evidence of a fracture of the neck of the femur, with dislocation of the head. The second was a woman aged 35 who had been 13 months on treatment, and whose functional status had risen from 4 to 2, the maintenance dose having been dropped from 100 mg. to 75 mg. She developed persistent oedema, increasing obesity, severe dyspepsia, headache, and casts in the urinary deposit.

One of the aspirin patients was a man aged 40 who had been 13 months under treatment, with a daily dosage of 60 gr.; because of persistent dyspepsia, even on 30 gr., the aspirin had to be withdrawn. The second withdrawal in this group was due to the patient's emigrating to New Zealand.

We still have seven cortisone patients on treatment: two are being well maintained on 50 mg. daily, without side-effects, the functional status having improved in one from 2 to 1, and in the other from 4 to 2. Two patients require 75 mg. daily for adequate suppression, but because they developed hypertension on this dose, a reduction was made to 50 mg. daily, with some recurrence of symptoms. One has attained partial but useful suppression of symptoms on 100 mg. daily and is able to do light work. Two require between 100 and 125 mg. daily for partial control and are still substantially handicapped, but they do not tolerate higher doses.

We have six patients still on aspirin: one is in clinical remission and is no longer receiving the drug, three are well maintained and can perform all normal activities, one flared up violently on treatment and was re-admitted to the hospital, but is again well controlled on 90 gr. daily, the last has steadily deteriorated throughout the period of trial on a dose of 60 gr. daily.

Thus, with aspirin we have five reasonably satisfactory results and one deterioration during treatment; with cortisone four are satisfactory and one is fair, while in two cases the drug has had to be withdrawn because of side-effects.

With regard to less serious side-effects, the aspirin group have all had dyspepsia or tinnitus with high dosage, but this persisted only in one, from whom the drug was withdrawn. In the cortisone group three have oedema and hypertension limiting dosage, one female has developed amenorrhoea, gained in weight, and lost hair, two have obvious mooning of the face, and in two there is some emotional instability.

The effects on haemoglobin at the end of one year were much less striking. It improved in the cortisone group by 8·5 per cent., and in the aspirin group by only 1 per cent. The blood sedimentation rate in the cortisone group has dropped an average of 38, and in the aspirin group an average of 23. It does not appear therefore, in this small group, that the results at the end of 1 year differ from those reported for the whole group at the end of 3 months.

DR. CHARLES RAGAN (*New York, N.Y.*): One can have only admiration for this excellent statistical treatment of rheumatoid arthritis. There is, however, one feature of the study which concerns me, namely, the use of early cases. There is no real answer to this problem, since Drs Hill and Kellgren have clearly stated that they wished to study disease activity rather than symptoms resulting

from deformities which would enter the picture in late cases. The early case is, nevertheless, a treacherous subject, and all of us are fully aware of this pitfall. From a clinical impression, which is a poor substitute for an accurate statistical study, one would expect a fair number of spontaneous remissions in such a sample during one year, and both Dr. Duthie and Dr. Kellgren had one.

Dr. Kellgren stated that the dose ceiling for aspirin was the same at the beginning of treatment as at the end. A word of caution should be said in regard to this. Tinnitus and deafness due to salicylate administration are relatively safe when the patient is under close observation in a hospital. On an ambulatory basis, however, when the patient is seen once a week, we are reluctant to carry a patient at the level of deafness, since with relatively little stimulus he may swing over into salicylism with overbreathing and a respiratory alkalosis.

DR. PHILIP R. TROMMER (*Philadelphia, Pa.*): I should like to point out that in statistical studies of this type it is perhaps best to carry out, besides a single blind test, a so-called "double blind test" in which placebos are used which will take into account the natural course of the disease in a good many of the patients.

DR. CHARLES RAGAN (*New York, N.Y.*): I think it is now fairly well established that aspirin is an anti-inflammatory drug, and not solely an analgesic; it will suppress an inflammatory process to some degree.

DR. DONALD F. HILL (*Tucson, Ariz.*): I want to congratulate our colleagues from England. We have now had cortisone for 3 years, and have been studying it from every angle. These gentlemen are attempting, not a 6 or 13 weeks' study, but a long-term experiment over the next several years, comparing the results of aspirin and cortisone, of which the present report is only preliminary. I have not heard of any other study like that which has been outlined comparing cortisone with aspirin or anything else for such a long period.

PROF. BRADFORD HILL: We endeavoured to allow for differences in assessments, etc., by having equal numbers on each treatment at each centre. Though the numbers are small we also inspected the results found at each of these separate centres and we could nowhere observe any material difference between the cortisone and aspirin groups. On the whole the *equality* of the results with the two treatments is the most striking aspect so far; it seems unlikely that differing judgements at various centres could have brought about such an equality in the total. In a multi-centre trial we can at least take some steps to ensure uniform criteria and judgements. When individual centres frame their own schemes no such uniformity will necessarily result and comparisons from one centre to another (such as appear in the literature) become still more difficult to interpret. In such a long-term trial of the treatment of early cases of rheumatoid arthritis we held a "dummy" treatment to be quite out of the question on ethical grounds. We do not, of course, set out to treat a case of rheumatoid arthritis, or any other disease, "statistically". In the clinical trial we are concerned only with groups and groups can be made remarkably alike so that we may see how the patients respond to different treatments. There is no way of telling, statistically or clinically, how any individual will respond. That requires crystal gazing or second sight. The clinician, in fact, is observing group reactions. He notes the reactions of a patient to a certain treatment and uses the treatment again to see whether that result recurs. In such trials as this we are merely trying to make such observations more precise and better controlled, the comparisons more exact and less impressionistic.

DR. KELLGREN: In answer to Dr. Ragan's comment on the early cases, it is true that remissions do occur in early cases, and that is why we included one week of no treatment every quarter. Had we not done so, it would have been very difficult to know whether the improvement in function we were observing was due to the treatment we were prescribing or to the natural history of the disease. The deterioration during each week of no treatment at the end of each quarter, and the improvement in function when treatment was resumed gives a clear answer that the improvement must have resulted from the treatment and not from spontaneous remission.

We also chose early cases because we wanted to see whether long-term therapy with either of these two remedies affected either the progress of the disease, or the number of spontaneous remissions.

We chose subjective criteria because the first object of the trial was to compare these two substances as symptom suppressors as agents for allowing the patient to do more, to go back to work, to go up and down stairs better, to use his hands better. Those are all subjective criteria, but what matters is whether the patient is able to work or is bedridden.

We do not say that cortisone and aspirin have precisely the same effect on the rheumatoid process. In fact the reverse is the case, since the effects on sedimentation rate are different, and also, as Dr. Steinbrocker pointed out, the patients feel better and eat better on cortisone. But these differences do not seem to have affected the patients' capacity to work or general functional status.

Joint swelling was a subject which we considered at great length; we did think of including it, but finally rejected it, because some of these early cases had very little swelling, and also we had difficulty in finding a standard method of measuring so many different joints. If all the patients had had involvement of the fingers, we could have used rings, but in some of them the feet and ankles were involved and these joints are not so easily measurable.

We are, in fact, studying other things as well as subjective criteria. We are taking *x* rays before treatment and at a much later date, but a 3 months' interval is not likely to show any difference, and we cannot yet say what has happened in the joints.

Panel Discussion: American Rheumatism Association Cooperative Study of Cortisone Therapy in Rheumatoid Arthritis.

DR. MCEWEN.—At the last meeting, when the panel on rheumatic fever was presented in co-operation with the American Council on Rheumatic Fever, it aroused considerable interest and the suggestion was made that it might be worth while to carry out a similar study on the effect of cortisone in rheumatoid arthritis. It was left to me as President of the Association to organize this panel, and frankly I was so sceptical of its feasibility that I postponed calling together a committee until the regularly scheduled meeting of the Executive Committee of the Association, which is held in November.

The day before the regular meeting of the Executive

Committee, a group was asked to discuss the feasibility of this plan. That committee consisted of Drs. Bunim, DeForest, Freyberg, Kammerer, Ragan, Robinson, Rosenberg, Short, Slocumb, Charley Smyth, Ziff, and myself, for the clinicians, and Dr. Donald Mainland and Mr. Felix Moore, the latter of the United States Public Health Service, to give statistical guidance.

The committee thought that it would be worth while to get together some data, but decided that it would not be wise to undertake an ongoing or forward looking study, if I may use that term, like that on rheumatic fever, which included only new admissions, previously untreated. It was deemed preferable, since cortisone had been in use for several years and many records were already available in various clinics, to begin by seeing what might be learned by analysing the existing data.

A grant of $5,000 from the Arthritis and Rheumatism Foundation made this study possible and of the many workers who were invited to participate, the following joined the project:

Dr. Arthur W. Bagnall - - *Vancouver.*
Dr. Walter Bauer and Dr. Charles Short *Boston.*
Dr. Theodore Bayles - - - *Boston.*
Dr. Paul J. Bilka - - - *Minneapolis.*
Dr. Gideon K. DeForest - - *New Haven.*
Dr. Ephraim P. Engleman - - *San Mateo.*
Dr. Dwight C. Ensign - - - *Detroit.*
Dr. Richard Freyberg - - - *New York City.*
Dr. Wallace Graham - - - *Toronto.*
Dr. Edward Hartung - - - *New York City.*
Dr. Philip Hench and Dr. Charles Slocumb *Rochester, Minn.*
Dr. W. Paul Holbrook - - *Tucson.*
Dr. William H. Kammerer - - *New York City.*
Dr. John Lansbury - - - *Philadelphia.*
Dr. James Lightbody - - - *Detroit.*
Dr. L. Maxwell Lockie - - *Buffalo.*
Dr. Charles Ragan - - - *New York City.*
Dr. William Robinson - - - *Ann Arbor.*
Dr. Edward Rosenberg - - *Chicago.*
Dr. Richard T. Smith - - - *Philadelphia.*
Dr. Charley J. Smyth - - - *Denver.*
Dr. Robert M. Stecher - - - *Cleveland.*
Dr. Otto Steinbrocker - - - *New York City.*
Dr. Morris Ziff - - - - *New York City.*

A total of 446 records have now been received, which are considered suitable for the study. The central committee drew up a form which could be used for the tabulation of data in each case, so that all the information could be entered in a comparable way in a summary sheet which could be subjected to analysis in the central office. Miss Claire Lingg, staff statistician, with Mrs. Esther Bigus, did a splendid piece of work in putting the data together for analysis in a very limited time. I should like to emphasize that this report is a rush job, and that it is preliminary not only in the sense that not all of the data have yet been received, but also that only partial analysis has this far been possible.

The criteria of the Steinbrocker-Traeger-Batterman report, which has been adopted by the Association, were used to standardize the various cases as to stage and class of disease and grade of response.

Early in the study the following criteria for accepting patients were decided on:

(A) Patients must be straightforward rheumatoid arthritis cases.*

(B) Cortisone must have been the main therapeutic agent used.

(C) The arthritis must have been present for at least six months before the administration of cortisone.

(D) Only patients must be included who have been observed by the participating physician for a period of at least 1 year since the initiation of cortisone, and the patient must have received cortisone *continuously*,† on minimum dosage of 15 mg. daily with the following exceptions:

(*i*) dosage stopped because of sustained remission,
(*ii*) dosage stopped because of toxicity,
(*iii*) dosage reduced or discontinued temporarily for observation of the patient's response,
(*iv*) dosage discontinued because of inadequate benefit to the patient.

The *pro forma* used for recording information included:

Diagnosis;
Date of starting cortisone;
Whether the onset was before, during, or after menopause;
Dosage, in approximately daily averages by months;
Time of onset of the disease and of the present attack;
Joints involved;
Other diseases present at start of cortisone;
Previous therapy, with physician's opinion as to its effect;
Concomitant therapy given with cortisone, and physician's opinion as to its effect.

The *pro forma* also showed:

Result of treatment by months, showing stage, class, grade, and any changes that may have occurred;
Changes in weight, blood pressure, sedimentation rate, and haemoglobin;
Whether cortisone was stopped permanently and if so, when and why—whether because of remission, partial remission, inadequate benefit, because the patient was worse, because of toxicity, or other reason;
Whether nodules or psoriasis were present;
Side-effects (significant and "minor");
Follow-up: whether patient was still under observation, had died (if so, cause of death), or had left the study (if so, reason).

* It is desired to take into the study patients with spondylitis and psoriatic arthritis for subsequent analysis, but it was thought that at first, in the short time we had, we should limit the analysis to patients with classical rheumatoid arthritis.

† "Continuously" is defined, for our purposes, as including those patients who may have stopped temporarily for periods of time, but in whom the intent was continuous treatment.

Dr. Mainland, who was a great help to the committee throughout the study, set out certain precautions and limitations at the beginning.

We can start the panel in no better way than by asking him to comment briefly on these limitations and precautions.

DR. DONALD MAINLAND (*New York, N.Y.*): In the paper by Dr. Bradford Hill and Dr. Kellgren we have just heard a good account of a modern clinical trial.*

A modern clinical trial is an experiment, but what we are going to present is a report on a survey of physicians' experiences and impressions. At one time it would have been thought that a survey of this kind was the proper, perhaps the only, method of ascertaining the effectiveness of a therapeutic procedure. Nowadays we are coming to see that it is a very inferior method. That statement does not cast any reflection on the competence of the physicians who supply the information on which the survey is based. The weakness is inherent in the survey method itself.

Therefore, we on the committee must emphasize that we were not trying to substitute a survey for a modern clinical trial. Our five objectives, laid down at the outset, and repeatedly referred to, were as follows:

(1) To obtain information that would enable the Association, or other groups, to decide whether a controlled comparison of various treatments of rheumatoid arthritis is feasible, and if so, how it can best be planned.

(2) To ascertain the experience of certain clinics during a certain time period (set at 3 years) in the treatment of rheumatoid arthritis by cortisone; not to assume that these findings were true for other clinics or other physicians at the same period, or applicable now or in the future. (One reason for this proviso was the change in clinical judgement that has occurred during the last 3 years regarding the suitability of cases for treatment.)

(3) To look for differences in response that may appear to be associated with certain features, such as age, sex, pregnancy, duration of disease before treatment, concomitant treatment, and so on; not to assume that such appearances are anything more than a hint of a possible association.

(4) To look for differences between the statements of different clinics regarding outcome, and to seek for hints of possible explanations; not to pursue this search very far, because of the numerous undiscoverable factors undoubtedly present.

(5) To form an impression of the facilities of the clinics, and their suitability for possible co-operation in a controlled comparison of different treatments.

The fifth objective refers particularly to the numbers of patients available and to the types of records kept, and in this connection we must point out that we were not trying to set ourselves up as critics of those who kept the records. We were aware that we were trying to use these records for a systematic investigation for which they had not been designed.

There is one defect in records which is inherent in all such surveys, namely, the progressive loss of patients from a series. It is very dangerous to assume that those lost sight of are equivalent in response to treatment, or in any other feature, to those who remain in the study. That is why, in looking at our figures, we should pay much more attention to the first 12 months than to the longer period.

The incompleteness of records, serious though it be, is not the only weakness of the survey method. In a properly conducted experiment we distribute the factors under test, such as the different clinical treatments, strictly by chance, and then during the experiment we take the necessary precautions to prevent bias entering in. At the end, if we are successful in so doing, we are able to say that either the factor under test was responsible for the outcome or that chance was responsible. There is nothing else in the experiment.

If this sounds like a lecture on statistical method, I can assure you that I am not going on much further, but we have to consider this one statistical principle, which is becoming commonly accepted in all fields of science at present as the basis of any properly controlled experiment. If at the end of such an experiment we can say that chance operating alone would rarely cause such a big effect, then we may feel reasonably confident that the effect was due to the factor that we were testing.

Now, by contrast, in seeking for a cause and effect relationship after a survey, we have to say that the factor we are investigating, or chance, or some other factors not allocated by chance, might be responsible.

To reduce the risk of bias from such other factors, we can divide up the data in various ways into appropriate sub-classes: duration of disease, concomitant treatment, degree of improvement if any, different physicians, and so on. But even if we had sufficient material for this, and even if the records were absolutely complete, we should still be left with the possibility of unknown factors. For practical purposes, in some cases we should not worry very much if we could carry the analysis so far, but in the present work we cannot, because of our data (not only number but type of data), approach nowhere near that stage of analysis.

Therefore, in presenting these figures to you we are conscious of a grave responsibility which we must ultimately bear to your patients if we show you something which influences your methods of treatment in the wrong direction. Simple figures and especially simple graphs are very dangerous things.

We have tried to be very careful, and you may be somewhat disappointed when we refuse to commit ourselves, or admit that we have no data on such and such an item. At the outset we decided that we must limit drastically the information requested from those who helped us in the survey.

In spite of these and other deficiencies, we believe that we have obtained a useful picture of what has been going on during the past 3 years. Our exploration of the ground may well lead to a further experimental investigation. We have learned, partly through our own mistakes, a good deal about how to frame a question sheet for such a complicated disease as rheumatoid arthritis.

* I should like to say parenthetically that if anyone wishes to learn more about such trials in general—and we all should—he could do no better than read Professor Bradford Hill's article in the *New Engl. J. Med.* (1952), **247**, 113.

Finally, we have learned how much pressure a very skilful statistician, such as Miss Lingg, can tolerate. We estimate that 14 hours a day of steady work on these very confusing data bring her near her tolerance limit. So if you ask us questions and we have to turn to her because we don't know the answers, I think you will sympathize with her if she displays some signs of toxicity, some kind of mental indigestion.

We owe very much to Miss Lingg, and we are very anxious that none of the deficiencies of the survey should reflect on her. If you must shoot, please aim at us and not at Miss Lingg.

DR. MCEWEN: We will turn now to a series of five brief presentations of some data.

(1) DR. G. K. DEFOREST (*New Haven, Conn.*): I think it is generally accepted that rheumatoid arthritis is a disease which is found most commonly among people in the middle age group, and more commonly in women than it is in men.

Our 446 patients represented a fairly average sample of a rheumatoid arthritis population in age and sex, most of them being beyond the age of 45. Fifty per cent. of them had had the disease less than 6 years, and 75 per cent. less than 12 years when the study was begun.

Each patient was graded in four "Stages" of disease (Stage I being the mildest, and Stage IV the most severe); and in four "Classes" of functional capacity (Class I representing complete functional capacity, and Class IV severe incapacity). About 70 per cent. of our 446 patients were in Stage II or III, and in Class II or III.

DR. C. H. SLOCUMB (*Rochester, Minn.*): We recorded the patients' evaluation of the effects of therapy received *before* this study was started.

Gold had been used in 273 patients; 43 per cent. reported "improvement" and 46 per cent. "no improvement".

Cortisone and corticotropin had been used in 56 and 71 patients respectively before this study with cortisone was started; "improvement" was reported in 82 per cent. and 90 per cent. of the two groups, and "no change" in 16 and 9·9 per cent.

Many other treatments had been tried in 144 patients, and 68·7 per cent. reported "no improvement".

We also recorded the investigators' opinion of the effectiveness of concomitant therapy given *during* the study. This therapy was given either at the same time as cortisone was administered or during intervals when cortisone was not being administered.

Gold, used in 102 cases, was reported to have been "helpful" in 30 per cent., "not helpful" in 26·5 per cent., and "of doubtful value" in 38 per cent.

Intra-articular Compound F, used in 124 cases, was reported to have been "helpful" in 63 per cent. (for how long, is not recorded for each patient), "not helpful" in 17·7 per cent., and "of doubtful value" in 16·9 per cent.

Corticotropin, used in 63 cases, was "helpful" in 46 per cent., "not helpful" in 25, and "of doubtful value" in 23 per cent.

Salicylates, used in 312 cases, were reported as "helpful" in 85·6 per cent., "not helpful" in 6 per cent., and "of doubtful value" in 9 per cent.

Butazolidin, used in 96 cases, was reported as "helpful" in 36·5 per cent., "not helpful" in the same percentage, and "of doubtful value" in 24 per cent.

Neither the severity of the cases nor the criteria of improvement are necessarily comparable. If a certain drug helped a little at the time, irrespective of the shortness of the duration, it may have been recorded as of some help, but this cannot be compared with the *general* improvement or lack of improvement which may have taken place in the patient while taking cortisone.

DR. MCEWEN: Although it has already been said several times, we must emphasize again that the foregoing do not represent anything more than a Gallup poll of the opinions as to helpfulness which were expressed by patients and investigators.

(2) DR. CHARLES RAGAN (*New York, N.Y.*): We divided the patients according to the severity of the disease into three groups:

Group A: Stages I and II, Classes I and II;
Group B: Stages I and II, Classes III and IV;
Group C: Stages III and IV, any class.

In other words, A are the patients with mildest disease; B those with moderately severe disease; and C those with the most severe disease.

Dosage.—About two-fifths of the patients (40 per cent.) received not more than 50 mg. cortisone a day as their approximate daily average dosage after the first 3 months of therapy. 60 per cent. received more than 50 mg. a day. It must be stressed that in each group there are wide differences: "under 50 mg." can range from 12·5 to 50; "over 50" can range from over 50 up to 200. There was no set dosage schedule.

You must note that objectives of therapy varied and that regulation of therapy depended upon the judgement of the individual investigator. It may appear that the patients with more severe disease received larger amounts of the hormone, but Dr. Mainland refuses to say whether this observation has statistical validity.

Duration.—100 per cent. of the patients received cortisone at the start—in other words, 446 patients. During the first 6 months of the study cortisone was stopped, in 10 per cent. of the patients; 75 per cent. of the total continued to receive cortisone for at least 12 months, and 35 per cent. for 24 months. There were two reasons for this:

In the first place, some patients came into the study only in the past year or so. As a requirement for a patient's entry, it was necessary he should have started on one year before the study was completed, or before the preliminary report was given, so everybody has not been observed for these 12 months.

On the other hand a certain number of patients have dropped out of the study and been lost. Very few patients come into the full 3-year range, and the number in the 2-year range is much less than that in the 1-year range.

Withdrawal.—In 214 patients (48 per cent. of the total)

cortisone was stopped; in 28 patients (13 per cent.) it was stopped because of remission, but of these 28, only twenty were listed as Grade I remissions when the cortisone was stopped, and the other eight were Grade II.

In 41 patients (19 per cent.) cortisone was stopped in a partial remission; there was no change in grade in sixteen of them, and twelve subsequently reverted to a lower grade after withdrawal of the drug.

Inadequate benefit was given as the reason for stopping cortisone in almost 30 per cent. This again reflects the bias of the individual investigators, since opinions as to what constitute inadequate benefit may differ.

"Patient worse" was reported in 6·1 per cent. as the reason for stopping cortisone, toxicity of one sort or another in 14 per cent., and other causes* in about 18 per cent.

No record was obtained in 0·5 per cent.

(3) Dr. William H. Kammerer (*New York, N.Y.*): The committee decided at the outset to divide the undesirable side-effects that might be attributed to cortisone into two groups: minor and major. It is recognized that opinions on what comprises a minor or a major side-effect will differ with individual clinicians.

Incidence.—30 per cent. of the patients had no minor side-effects. As might be expected, the incidence was almost double in patients receiving more than 50 mg. daily as compared with those receiving less than 50 mg. daily.

These minor side-effects are mostly those of the hypercortisone state, except for emotional instability and excessive fatigability, which may in some instances be manifestations of the rheumatoid arthritis rather than the results of cortisone toxicity.

When a breakdown of these patients by age and duration of disease is available, it may show some significant differences in these respects. Cortisone was not stopped in any patient in the group with minor undesirable side-effects. The menstrual irregularity mentioned in this connection does not apply to the whole group of patients, but was confined to 139 women who were thought to be pre-menopausal.

48·2 per cent. of patients had no major side-effects; the incidence was higher in those receiving the higher dosage, but the difference is not quite as striking as in the survey of minor side-effects. In approximately half of this latter group it was felt necessary to discontinue therapy. The drug was not withdrawn from patients who developed glycosuria, but it was withdrawn in approximately 54 per cent. of those who developed a peptic ulcer, and in 50 per cent. of those with psychosis.

(4) Dr. Richard Freyberg (*New York*): When we analysed the response of rheumatoid activity to cortisone, the results were graded according to the criteria of the American Rheumatism Association:

Grade I: complete remission;
Grade II: major improvement;
Grade III: minor improvement;
Grade IV: no change.

The grade of response was ascertained at four different periods after beginning cortisone treatment: 6, 12, 18, and 24 months. These figures do not imply that the patients were always receiving or continuing to receive cortisone through that period; they define the length of time that the patient was observed after the start of cortisone.

After 6 months, approximately 90 per cent. were continuing to receive cortisone. After 24 months, approximately 60 per cent. had been continuing to receive cortisone, but in some, it had been discontinued for different reasons.

Some patients were observed for as long as 36 months, but this number was insufficient to be subjected to analysis.

At the end of 6 months of observation after the start of cortisone, of the 82 patients in Group A,* there were 12 per cent. in which the record was insufficient, 8·5 per cent. in Grade I, 46 per cent. in Grade II, 24 per cent. in Grade III, and 8·5 per cent. in Grade IV.

By contrast, of the patients in Group C, 2·6 per cent. showed Grade I response, 30 per cent. Grade II, 44 per cent. Grade III, 15 per cent. Grade IV. In the intermediate Group B, the results also are intermediate.

The second important fact appeared when we compared the three different groups of patients at the end of the four different periods of time, and it seems most striking that at the end of 12, 18, and 24 months, as compared with 6 months' observation the results in each group are similar.

With the patients observed for the longest period, 24 months after the start of cortisone, the following points were apparent: In Group A there was a slightly larger number of cases (14 per cent.) in Grade I (complete remission); Grade II response was seen in 49 per cent., Grade III in 20 per cent., and Grade IV in 4·4 per cent. Similarly, in 157 Group C patients, there were fewer (3 per cent.) in complete remission, and 28 per cent. in Grade II. The largest percentage (40 per cent.) occurred in Grade III, and there were also more in Grade IV. So that here also, 24 months of observation after the start of cortisone, with 60 per cent. of the patients continuing to receive cortisone all that time, the response is similar to that seen in the short period of observation, the less sick patients having a higher percentage of better response.

I must remind you that different patients received varying doses of cortisone, and the data has not yet been analysed in regard to different dosage level.

The committee thought it would be instructive to analyse the data from the standpoint of one therapeutic change, namely functional capacity, and to trace this change in each group at the end of 6, 12, 18, and 24 months. This change was observed in three different groups of patients:

* About one-third of these could be ascribed to toxicity, which would bring the toxicity figure to about 21 per cent., and the other reasons were financial or domestic.

* See p. 332 for definition.

Group 1: Cortisone was stopped sometime during the period of observation because of sufficient benefit;
Group 2: Cortisone was stopped because of some unfavourable effect;
Group 3: Cortisone was being continued.

Class I: able to carry on all usual duties;
Class II: able to conduct normal activity despite handicap or discomfort;
Class III: with limited functional capacity, able to perform very few of the duties of usual occupation or self-care;
Class IV: completely incapacitated;
NR: insufficient data.

Group 1 (69 patients).—Many patients were in Class II, more were in Class III, and some were incapacitated at the beginning of treatment. After 6 months' observation, there was a change in functional capacity to Class I in 29 per cent., and to Class II in 54 per cent.; a few remained in Class III, and very few in Class IV.

Those who changed from Classes II and III, changed into Classes I and II. At the end of 12 months, 67 patients remained under observation: 40 per cent. had changed to Class I and 43 per cent. continued in Class II. After 18 months we found a similar percentage in different classifications, and after 24 months, slightly fewer in Class I, with little change in the other classes.

It seems clear from this analysis that in Group 1 definite improvement in function occurred, and was quite well maintained up to 24 months.

Group 2 (44 patients).—Most of these persons started in Class III. After six months of observation, 7 per cent. had changed to Class I, and there were 46 per cent. in Class II, and 36 per cent. in Class IV. After 12 months, we found little further change. After 18 months, there was some decrease in Class II, and after 24 months little change.

Group 2 therefore shows distinctly less improvement as measured in functional capacity than Group 1. That seems quite reasonable, because since some unfavourable result of cortisone administration had required its discontinuance, these sick persons continued to be sick, or, in fact, became worse when cortisone was discontinued. Yet it seems of interest that certain improvements in functional capacity were maintained from 6 to 24 months.

Group 3.—All the patients in this group received cortisone without interruption for the different period up to 24 months. After 6 months there was 12 per cent. in Class I, 55 per cent. in Class II, 25 per cent. in Class III, and 7 per cent. in Class IV. This improvement was maintained with little change throughout the 24 months, and there were slight increases in the numbers of those who improved as time went on. In this group, too, therefore, the improvement seen in the first 6 months seemed to be maintained in the 24-month period.

The comparison of these three groups of patients shows greater functional improvement changes in Group 1, and less in Group 2, while Group 3, who were continuing on cortisone, showed an intermediate degree of response.

(5) Dr. Morris Ziff (*New York, N.Y.*): The patients who were still under observation at various times after starting cortisone are divided into three categories:

(*i*) those still on cortisone (Group 3);
(*ii*) those who stopped for favourable reasons (Group 1);
(*iii*) those who stopped for unfavourable reasons (Group 2).

The percentages of patients in these categories are listed at intervals from 6 to 36 months. As time went on, the number of patients under observation became steadily smaller, and after 3 years we had a very small group of 28 patients, a number which we do not consider significant.

The reasons for stopping therapy have been previously defined by Dr. Ragan. Favourable reasons for stopping included remission and partial remission. Unfavourable reasons included inadequate benefit, deterioration, and toxicity.

Analysis of the data indicates that in the 24-month and 36-month periods, about 25 per cent. of the larger groups had left observation. 236 are listed as under observation for 2 years, but a total of 315 had been started on cortisone therapy, and of these, seventeen (5 per cent.) had died, and 59 (20 per cent.) had left the study.

By the end of the first 6-month period, 90 per cent. of the patients were still on cortisone. About half of the 10 per cent. who had stopped had done so for favourable reasons and half for unfavourable reasons.

At the end of 12 months, 80 per cent. of the patients were continuing on cortisone, 20 per cent. having discontinued therapy. As time goes on, the percentage of patients on cortisone becomes gradually smaller, and half the patients seem to have stopped for favourable, and half for unfavourable reasons. At the 24-month period, we have 60 per cent. of the patients still on cortisone.

About half of the small group of 28 patients who were observed for 36 months, had continued on cortisone.

In the entire group of 446 patients, there were 26 deaths. Eight patients died while receiving cortisone, and eighteen patients died after cortisone therapy had been discontinued. Six of the eighteen died within one month after cortisone was stopped; thus fourteen out of eighteen patients (53 per cent. of the group who died), did so either while receiving cortisone or within a month after

it was stopped. We have broken down the deaths into age groups:

over 70—8
60-70—8
50-60—6
42-50—4.

The causes of death were as follows:

Coronary thrombosis, 3;
Cerebral vascular accident, 6;
Pulmonary infarct, 1;
Congestive heart failure, 4;
Pneumonia, 2;
Bacteraemia, 1;
Acute bacterial endocarditis, 1;
Carcinomatosis, 2;
Pancreatitis, 1;
"Malignant" (diffuse, systemic) rheumatoid arthritis, 2 (one died while on cortisone, and one died when cortisone had been stopped for quite a while);
Accident, 1;
Shock during administration of anaesthesia, 1 (this occurred in a 50-year-old patient who had been on cortisone 13 months, cortisone having been discontinued pre-operatively).

At present, 358 patients (83 per cent. of the original group) continue under observation; 62 (14 per cent.) have left the study, and 26 (about 6 per cent.), are dead.

DR. MCEWEN: That concludes the summary of the data so far collected. Believe me, the committee is fully aware of the limitations.

It might have been better to have compared cortisone with the salicylates, for example, as has been done in the United Kingdom study. But since ours is not a forward-going study, but an analysis of data already available in the various clinics, that was not possible.

Certain members of the committee are taking part in this panel and others are not, chiefly through accidents of time and geography. It was necessary to have rehearsals the day before yesterday, and only those members of the geographically widely-scattered committee who could be present on that day were able to acquaint themselves with the available data.

A statement summarizing the data was approved by the committee, and this I now propose to read.

STATEMENT OF THE CO-OPERATIVE STUDY OF CORTISONE IN RHEUMATOID ARTHRITIS BY A COMMITTEE OF THE AMERICAN RHEUMATISM ASSOCIATION

To obtain data on the effects of cortisone in rheumatoid arthritis in larger numbers of patients than are available in the experience of any one observer, this committee of the American Rheumatism Association was appointed in November, 1952, to explore the feasibility of obtaining data on a co-operative basis from a number of clinics: 27 physicians, all members of the Association and representing 25 clinics in all parts of the country, have contributed data on 446 patients with rheumatoid arthritis who have been observed for periods of 1 to 3 years from the start of treatment with cortisone.

The preliminary data available indicate that cortisone has a beneficial effect in improving the functional condition of many patients with rheumatoid arthritis and in reducing the evidences of inflammation. These benefits were greater when treatment was begun when the disease was less advanced. Of the 446 patients, 232 continued to receive cortisone during the period of observation. In 32 per cent. of the remaining 214 patients in whom cortisone was discontinued, the hormone was stopped because the physician considered improvement had advanced to a point where cortisone was no longer needed. In the other 68 per cent., the hormone was discontinued because of undesirable side-effects, or because the patient was not thought to be improving, or for financial (or other) reasons. Undesirable side-effects were considered to be of major significance in 47 per cent. of the total number of patients at one time or another during treatment, but in only 18 per cent. of the total of 446 did the physician deem it necessary to discontinue treatment for this reason.

The results so far obtained are of sufficient interest and importance for the study to be continued to obtain more definite information on a larger number of patients.

Having completed our part of the presentation, we should now like to have questions from the rest of the Association.

DR. JEROME SIMSON (*Forest Hills, N.Y.*): I should like to ask Dr. Kammerer whether the side-effects are related to age of the patient, duration of the disease, or salt-restricted diet, or whether there appeared to be no reason at all for their occurrence.

DR. KAMMERER: Unfortunately, these have not yet been analysed from a statistical standpoint, but I think they may well show significant differences in these various categories.

DR. ROBERT W. QUINN (*Nashville, Tenn.*): I should like to ask Dr. Mainland why a group that received no treatment whatever was not also studied.

DR. MCEWEN: I will answer that for Dr. Mainland, if I may. The decision of the committee at the beginning was that it would not attempt to make a comparison of one form of treatment with another. In the opinion of the committee, such a comparison would be valid or permissible only in a forward-going study in which all the patients were observed according to reasonably uniform conditions, such as is being done in the United Kingdom study.

This study is only a survey, and that it was based on an analysis of data which had already been collected during

the previous 3 years. It was impossible for us to go back and set up uniform conditions for comparisons of that kind.

DR. J. J. R. DUTHIE (*Edinburgh, Scotland*): Has the committee reached any decision that it is now necessary to do that?

DR. MCEWEN: That is a question which the committee has to make up its mind about, at a meeting tomorrow. The United Kingdom study is bound to have a very definite effect on the attitude of the committee. Among the various reasons for undertaking this study, which Dr. Mainland outlined, was to help decide whether a forward-going study of the type now going on in the United Kingdom should be carried out. Two other reasons for undertaking the study will, I hope, also prove to be useful:

One was to get together information about a larger number of patients than would be available in any one clinic. This will undoubtedly prove valuable, and the larger number will include variants of rheumatoid arthritis, as well as typical patients with peripheral joint involvement.

We also hope to develop an established procedure which may be adapted to the evaluation of other agents that may be considered in the future. There is certainly need for a method of arriving at a quicker decision on new therapeutic agents.

DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): At the end of 24 months' observation, a higher percentage were in Grade I improvement than were after the 6-months' period. I cannot help but feel that this is due to some chance selection of patients, and I think the statisticians probably should try to work that out, because I doubt that there is a single man in the room who believes that, if you put fifty or one hundred patients on cortisone to-day, more of them would be in Grade I in 24 months' time than would be in 3 or 4 months from now, let alone 6. It has been our experience that the highest number of Grade I improvements occurs within the first 6 months, and that there are many fewer at the end of 24 months. I call that to your attention for some future explanation.

DR. MCEWEN: Dr. Freyberg, will you answer that?

DR. FREYBERG: Dr. Holbrook is calling attention to the apparent increase in the percentages of patients in both Group A and Group C who were observed to exhibit Grade I response (complete remission) after an observation period of 24 months, as compared with the much smaller percentage of patients in these two groups who showed Grade I response after 6 months from the beginning of cortisone therapy. Bear in mind that at the end of 6 months about 90 per cent. of the patients were continuing to receive cortisone. Of those observed at the end of 24 months from the start of treatment, only about 60 per cent. of the original group were still receiving cortisone.

Now, the number of patients in Group A was 82 at the end of 6 months, and 45 at the end of 24 months. The number of patients in Group C was 268 at the end of 6 months, and 159 at the end of 24 months. I believe that when the difference in those numbers is analysed, it will help to explain some of the differences in the percentages of Grade I response after different periods of time.

DR. BUNIM: Since there is so much interest in the difference in these two groups, at 6 months and 24 months, I think it might be well to consider this possible explanation. From the group of patients who have been carried for 24 months on cortisone, there have been deleted already, most likely, those who did very poorly and those who were not getting sufficient benefit from cortisone to warrant the continuation of the drug. That, therefore, eliminates the unfavourable cases, and might also explain why the number of patients who did worse, is smaller at the end of 24 months than at the end of 6 months. For the same reason, at the end of 24 months there was a higher percentage of patients who did very well than there was at the end of 6 months. This also brings out one of the indications for continuing cortisone for long periods in patients who do well on safe small doses without developing unfavourable toxic effects.

DR. FREYBERG: A word of caution as to how these data have been analysed. The different times of observation (6, 12, 18, and 24 months) refer to the period of observation of the patient from the beginning of cortisone. They do not necessarily indicate that the patients were still continuing to receive cortisone at that time.

There are a large number of factors that may contribute to explaining these differences that you see in the columns, but neither I nor the committee as a group is able to make any statement of explanation at present.

DR. MAINLAND: I think it should be pointed out also that this picture does not include patients who left the study.

DR. DONALD F. HILL (*Tucson, Ariz.*): How many patients remained in remission after withdrawal of cortisone, and for how long?

DR. ZIFF: I don't think we have that kind of data. We know the percentage of patients who were stopped for favourable and unfavourable reasons, but we have not worked out the percentage that remained in remission.

DR. MCEWEN: We do know that there was no change in grade in sixteen of the 41 patients who went into partial remission. Twelve subsequently reverted to a worse grade, but that is far from saying how long they remained in partial remission.

QUESTION: What do you mean by "remission"? Does that mean they have no stiffness?

DR. MCEWEN: For complete remission there had to be a Grade I response: that is, a complete absence of all

evidences of activity of the rheumatoid process. It is fairly obvious that this was not so in every case, because on some of the charts on which the individual observer recorded that the patient had gone into "complete remission", he called it a Grade II response. There were a few cases like that which did not exactly fit. This is one of the follow-up tasks which Miss Lingg will now undertake; namely, writing to inquire about individual patients concerning whom there is a doubtful statement on the chart.

DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): May I suggest to the statisticians that I think many of the men attending this meeting next year would like some kind of figure to show what has happened, at the end of 2 or 3 years, to 100, or 500, or 1,000 patients that are put on cortisone—in other words, a picture of the number of successes in relation to the total number, which we cannot obtain from the present data.

DR. MCEWEN: I am sure that the committee would welcome any suggestions. It is all too obvious that the present data are only preliminary. The study will go on, and much additional data can be obtained from the material already in hand or in process of compilation. No matter how we try to get the answers to all the questions that one would like to ask, there will still be questions next year, for which we shall not have thought to analyse the material. Any suggestions will be most helpful to the committee if you will tell us about them.

DR. H. F. KLINEFELTER, JR. (*Baltimore, Md*): I should like to ask the committee if osteoporosis was a complication of long-continued cortisone therapy.

DR. MCEWEN: We have observed it, too, but it was not one of the points that was analysed. At the present time there are studies going on, in the U.S.A., of smaller groups of patients, in which careful observations are being made on osteoporosis. I think the answer will be forthcoming, but I do not believe that we can get it out of the data of this particular study.

DR. J. H. KELLGREN (*Manchester, England*): Have you any information regarding the reasons why certain patients were started on cortisone in the first place? I think this may be relevant, because we all know that rheumatoid arthritis is a disease which fluctuates, with remissions and exacerbations over months and years. If cortisone was started because the patient was in a stage of exacerbation, then any subsequent follow-up will give you some patients who would have been in remission, and some who would have gone back to an exacerbation. At no time are all your patients likely to be in exacerbation, as they might have been at the first remission. Therefore, you may get the rather surprising state of affairs in which patients in whom cortisone was stopped for unfavourable reasons were still, on average, better than they had been before treatment was started, even a long time after the cortisone had been stopped.

DR. MCEWEN: What Dr. Kellgren said is correct. It is a point that influences data collected on the therapeutic value of any agent in a disease which is subject to ups and downs.

DR. FREYBERG: I want to re-emphasize in conclusion that the committee must caution the listeners that this is a collection of data and an analysis, and that we should not try to read too much into it.

DR. MCEWEN: It was not easy to put old data of this sort together, but I hope that in the end the results will prove worth the effort. I must again say that Miss Lingg has borne the brunt of the work up to now, and the committee offers her its thanks.

At this point in the proceedings the chair was taken by the new President, Dr. Charles Ragan.

Vascularity of the Early Subcutaneous Nodule of Rheumatoid Arthritis. By L. SOKOLOFF and R. T. MCCLUSKEY, *New York, N.Y.*, and JOSEPH J. BUNIM, *Bethesda, Md.*

The mature subcutaneous nodule of rheumatoid arthritis is an indolent lesion of which large amounts of necrotic detritus and scar tissue are the dominant components. In the early stages of its development, however, the nodule is highly vascular.

Seven cases illustrate four principal features of interest:

(1) Proliferation of vascular granulation tissue appears to be an early and integral feature of the development of the nodule.
(2) In several instances, it has been possible to demonstrate that the characteristic processes of necrosis and the formation of palisades of radially arranged, elongate cells occur about preformed as well as newly proliferated vessels. The necrosis at the periphery of the granulation tissue suggests that the process is a centrifugal one with respect to the vessels. The fact that the process of necrosis apparently follows the planes of the connective tissue about the vessels suggest that the necrosis-producing agent is fluidborne into them from the vessels.
(3) Inflammatory changes and necrosis may be seen within the vessels in these nodules and in the adjacent subcutaneous tissue.
(4) In several instances, the vascular lesions in the nodules occurred in individuals in whom it was possible to demonstrate the presence of similar arteritic lesions in striated muscle and synovial membrane.

These findings suggest that the blood vessels play a special role in the pathogenesis of the subcutaneous nodule, and that the occurrence of vascular lesions in the nodules is a local manifestation of a more generalized, specific rheumatoid arteritis.

Discussion.—DR. JOHANNES P. KULKA (*Boston, Mass.*): For several years we have been concentrating on collecting early rheumatoid lesions, and we were fortunate in obtaining six subcutaneous nodules which had been

excised within one week after they had become clinically apparent. Our findings bear out Dr. Sokoloff's suggestion that the systemic vascular changes of rheumatoid arthritis play a special role in the development of the nodules.

Dr. Sokoloff mentioned that the focal nature of the vascular lesions is one point favouring their specific origin. We found in a nodule of 4 to 6 days' clinical duration necrosis limited to a few adjacent cells in the wall of an artery. It is difficult to explain a lesion of such focal character as resulting from a non-specific secondary process.

In a nodule of 3 to 4 days' clinical duration, which came on during reduction of cortisone therapy, the dominant microscopic change was an intense angiitis with neutrophil infiltration of many minute vessels and the perivascular connective tissue.

In a nodule of 4 days' clinical duration the inflammation was confined almost entirely to blood vessels which, on serial section, turned out to be mostly venules. The patient had some unusually acute systemic manifestations and the diagnosis of rheumatoid arthritis was not fully established, but we have seen an identical venulitis in several entirely typical cases.

We owe a nodule thought to be of only 1 or 2 days' clinical duration to the alertness and co-operative effort of Dr. Howard Weinberger. Here there was a fairly well demarcated region, with the "geographic" outline typical of the focal necroses in fully developed rheumatoid nodules. In this instance, however, there was little or no necrosis and the region was characterized by oedema, deposition of fibrin-like material, and intense proliferation of fixed cells. In contrast to the surrounding hyperaemic connective tissue this region was relatively avascular and some of the vessels were thrombosed.

These regions that later on become necrotic, develop an intense oedema, some of it relatively poor in protein, while in other regions fibrin is found. The blood vessels were relatively scarce in the central region, perhaps because they were spread apart by the oedema of the accumulating exudate.

Under a higher-power microscope we can see how an intense proliferation begins in these areas of oedema. There were as many as three or four mitotic figures for a high-powered field, and these regions seemed to be proliferating at the rate at which sarcoma proliferates.

At this stage the fibrin looks like typical fibrin, and has not yet assumed the amorphous appearance of fibrinoid.

In this same early lesion the cells were protected right round the vessels. As long as the vessel is patent a few cells seem to remain alive around it, whereas once the vessel is occluded by thrombosis, it becomes the centre of the necrotic focus. This suggests that the necrosis is produced by ischaemia; where the ischaemia is kept at a minimum because the vessel is still partly patent, the cells seem to be protected.

DR. JAMES F. RINEHART (*San Francisco, Calif.*): This report is of considerable interest as I had been hoping to see some of the really early nodules of rheumatoid arthritis. I think the early change gives a clue not only to the histogenesis but also to the pathogenesis of the disease process. This substantiates ideas that I have had in the past that the lesion is primarily vascular. I think these acute necrotizing lesions are probably not constant or consistently found, but a less intense lesion leading to vascular occlusion is probably much more frequent.

These typical rheumatoid nodules with large zones of necrosis with palisading of cells at the border are really late lesions, and probably represent a degeneration of the connective tissue that has been formed during the process. To the pathologist, the necrotic zones in the classical nodule are very reminiscent of the gumma of syphilis, in which it is generally agreed that the necrosis results from vascular occlusion. It is much more important to spend time on the early nodules of rheumatoid arthritis than on the advanced phases of the disease.

DR. SHELDON SCHWARTZ (*Queen's Village, N.Y.*): It seems you have to be pretty sharp to pick up a nodule of such small size only one or two days' old. Typically one looks about the olecranon process for such a nodule. Do you feel this to be part of a generalized vasculitis, or know why nodules are so frequently found at this site?

DR. SOKOLOFF: If there is a morphological change that precedes the formation of the granulation tissue, we have not been able to ascertain its precise character other than that there appears to be a degree of oedema in the connective tissues. We have not been able to demonstrate with toluidine blue the so-called micunous, oedematous character described in rheumatic fever. We did not take special precautions to preserve metachromatic material with appropriate fixatives. That there is indeed an amount of metachromatic material in the areas involved in necrosis in the rheumatoid nodule, has been demonstrated by Drs Altschuler and Angevine. It is true that necrosis is not always seen in these vessels, but their association with the oedema in early stages of the lesion would provide an angiitic background for exudation in the development of oedema.

I don't know why, Dr. Schwartz, the nodules are located in the subcutaneous tissue in the region of the olecranon process. I suspect pressure, protracted shearing of some sort, traumatizes the vessels in a special way in each site. Why rheumatoid nodules have different locations from rheumatic fever nodules, which have so many similarities to the early rheumatoid lesions is a matter for speculation. Perhaps there are differences in the types of pressure exerted in the two types of patient, and perhaps, too, there are differences in the types of vessels of which we are unaware.

Histochemical Observations in Rheumatic Fever. By JAMES F. RINEHART, *San Francisco, Calif.*

Methods of histological demonstration of mucopolysaccharides or mucoproteins have enabled a more critical analysis of the early changes in rheumatic fever. Three histochemical methods have been applied in this study. One utilizes the colloidal iron, cochineal-fuchsin method. The second applies the Schiff reaction in combination with colloidal iron. The third is a fuchsin-aldehyde technique which stains sulphated mucopolysaccharides and other insoluble sulphur-containing substances. Utilization of the several methods enables clear differentiation of the various elements of connective tissue.

Tissues involved in rheumatic fever have a high mucopolysaccharide component, a portion of which appears to be sulphated.

The early rheumatic injury of the heart valves and

heart muscle involves a swelling of such substances. The "fibrinoid" changes appear to consist of fibrin and possibly other elements of blood proteins which have seeped into the mucoid material.

The implication of the morphological observations in the pathogenesis of rheumatic fever is briefly considered.

DR. B. Z. RAPAPORT (*Chicago, Ill.*): One should not permit this beautiful work to go by without some word about the importance of the study of the ground substance.

I should like to ask Dr. Rinehart what fixative was used in his preparations.

It has been our experience that the Altman-Gersh method of freezing and drying is preferable to the usual chemical fixatives because of the solubility of the mucopolysaccharides in the water of the fixative.

In a recent study of the ground substance of the nasal mucosa of hay fever patients before and after ACTH therapy, we found definite changes in the ground substance, the sub-epithelial, and the pericapillary basement membranes. If one used routine stains which do not demonstrate mucoproteins no histological differences were found in the tissues after treatment with ACTH. The Hotchkiss-McMannus stain demonstrated effects that could be attributed to condensation of mucoproteins of the ground substances and of the basement membranes of the sub-epithelial and pericapillary regions. These changes in the density of the basement membranes may indicate a part of the mechanism of improvement in allergy following the use of ACTH.

DR. KARL MEYER (*New York, N.Y.*): There is no question about the importance and the timeliness of such studies as Dr. Rinehart's. I wonder whether he has an explanation for this almost complete removal of the staining material by testicular hyaluronidase. In the heart valve, as well as in other loose connective tissue, we find at least two types, and possibly three different polysaccharides present; the one we call chondroitin B, the second chondroitin sulphate C, and the third is a fraction which resembles hyaluronic acid, although the quantity is small. Two of these (chondroitin sulphate C and this hyaluronic acid-like material) are digested by testicular hyaluronidase. The other is completely resistant, and this material is almost completely removed by testicular hyaluronidase, as Dr. Rinehart showed.

CHAIRMAN: I should like to ask how long this material was incubated in testing for hyaluronidase.

DR. RINEHART: Fortunately fixation for the colloidal iron technique is satisfactory with 10 per cent. formalin. Most of the material we studied was dug out of the files of the more active early cases of rheumatic fever. Using the toluidine blue metachromatic reaction one is apt to lose the metachromatic staining unless one is fussy about fixation and other features. Mercury bichloride will apparently stabilize the material to a considerable extent.

There is also no doubt that the mucoid material acts as a cement substance in blood vessels. A similar substance lies between muscle cells in most small arteries. The ground substance also forms, in part a support for the smaller blood vessels. I think the injury is to small blood vessels as well as to the interstitial mucoids.

I don't know why this material for the most part seems to have been removed by hyaluronidase. It may be that testicular hyaluronidase would not remove all the normal substance, while it might remove some of this that has been injured or partly depolymerized. It is a question that we should look into.

I cannot answer Dr. Ragan's question precisely. Some of this material was incubated for 2 or 3 hours, and some for as long as 24 hours.

Hyaluronidase of Animal and Bacterial Origin. By KARL MEYER, ALFRED LINKER, and BERNARD WEISSMANN, *New York, N.Y.*

Two distinct types of hyaluronidase have been recognized. We propose to call these animal or hyaluronidase A, and bacterial or hyaluronidase B. Both hydrolyse the hexosaminidic bonds of certain acid mucopolysaccharides, notably hyaluronic acid. In hyaluronidase A, the substrate affinity varies with the molecular weight. Testicular and snake venom hyaluronidases are examples of type A, the coccal and *Cl. Welchii* hyaluronidases are of type B. The end-product on prolonged hydrolysis of hyaluronic acid with hyaluronidase A is mainly a tetrasaccharide, accompanied by less than 10 per cent. of a disaccharide. The same disaccharide is obtained by N-acetylation of hyalobiuronic acid obtained by acid cleavage of hyaluronic acid, and is thus shown to be the repeating unit of the hyaluronic acid molecule. The end-product of the action of hyaluronidase B is a disaccharide (disaccharide B) markedly different in chemical and physical properties from the normal disaccharide. Disaccharide B contains one equivalent of *d*-glucosamine (isolated as the hydrochloride), an N-acetyl group, and one equivalent of uronic acid as determined by colour reactions and CO_2 evolution. Hyaluronidase B hydrolyses the tetrasaccharide (produced by hyaluronidase A), and yields one mole of normal disaccharide and one of disaccharide B. It is concluded from this and from other experiments that the action of hyaluronidase B consists of hydrolysis of hexosaminidic bonds accompanied by structural modification, probably of the uronic acid residue. The same reaction occurs when hyaluronidase B acts on partly desulphated chondroitin sulphate. It appears possible that the modified groupings produced by hyaluronidase B *in vitro* may also be produced *in vivo* when an enzyme from infected foci reaches connective tissues.

Discussion.—DR. JAMES F. RINEHART (*San Francisco, Calif.*): We should all be grateful to Dr. Meyer for this very basic work, it was largely this that started the ball rolling in what I think is the right direction.

The peculiar susceptibility, the peculiar relation of rheumatic fever to the haemolytic streptococcus is probably linked in some way to peculiar enzymatic and substrate reactions.

DR. ROBERT W. QUINN (*Nashville, Tenn.*): Does Dr. Meyer know whether any of these breakdown products are antigenic or can be made antigenic with the streptococcus.

DR. MEYER: We have prepared enzymatic digests, using a very short incubation period or very low enzyme concentrations and then fractionating the high molecular fractions. Thus far we have no data on the antigenicity of these fractions, which we want to study in human

subjects. There is naturally some reluctance to do this in patients.

Connective Tissue Studies in relation to Rheumatoid Disease. By J. H. KELLGREN, *Manchester, England* (by invitation).

Isotope studies of collagen metabolism in the rat, using C^{14} labelled glycine, have been completed by Dr. Slack of our research centre in co-operation with Dr. Neuberger of the National Institute of Medical Research. These studies suggest that collagens as a group have a very low turn-over, thus being largely outside the metabolic pool, and in this respect differing markedly from most other body proteins. In the adult tissues of old animals collagen is metabolically almost inert, while in young animals there is a laying down of new collagen to provide for growth and also a definite metabolic turnover. There are also tissue differences—the turnover being greatest in bone and least in tendon.

Although most of the connective tissue collagen and polysaccharide appears to be "fixed" in a rather stable complex, in certain tissues and in young animals there is a proportion of more soluble "free" collagen and polysaccharide, and it may be that the metabolic activity of the connective tissues is mostly in this component. If this were so, the metabolic activity of "fixed" collagen is likely to be very slight indeed.

In rheumatoid disease there are local destructive lesions of collagenous tissues, together with some generalized collagenous wasting and minute spots of fibrinoid change. Histologically a fibrinoid area shows a breaking up of the connective tissue fibres accompanied by an increase of amorphous material. When explored with an *x*-ray beam, fibrinoid areas fail to give the diffraction pattern of collagen, this being replaced by a diffuse ring with a spacing of about 4·8 Å. The electron microscope shows an increase of amorphous material and only a few degraded collagen fibrils or none at all. The hydroxyprolin content of fibrinoid is also extremely low. These findings suggest that in a fibrinoid focus the collagen has been lost and replaced by amorphous material which may be in the nature of a glycoprotein.

The main function of the connective tissues which form the supporting system of the body is to resist mechanical forces. This is achieved by maintaining a rather stable collagen polysaccharide complex, and any reduction of the stability of this complex is likely to lead to excessive connective tissue breakdown.

Discussion.—DR. WILLIAM S. CLARK (*Cleveland, Ohio*): In doing metabolic studies we have also been interested in this problem of the turnover of collagen, and of trying to determine whether it would be possible by balance studies to make similar calculations. Such studies are obviously not nearly so precise. Benedict showed years ago that a starving man will excrete nitrogen, sulphur, and phosphorus in proportion to the ratios of nitrogen, sulphur, and phosphorus in collagen free muscle. Many patients with rheumatoid arthritis are found to be in negative nitrogen balance. Calculation of a large pool of metabolic data on a number of such patients has shown that the ratio of nitrogen losses to phosphorus and sulphur is similar to or less than the ratios during fasting. Since sulphur and phosphorus are not known to be components of collagen, it would seem that there is no gross breakdown of collagen in rheumatoid arthritis by such methods of measurement. I should like to ask, incidentally, whether Dr. Kellgren has done any starvation studies to determine whether nutrition or the state of nutrition would alter the turnover.

DR. GEORGE G. HAYDU (*New York, N.Y.*): Dr. Kellgren's paper shows that collagen, not being in the same relation to metabolism as are other tissues, is most vulnerable. When some general metabolic derangement constitutes a quantitative change to other tissues, this same derangement could make a vital difference to collagen and the connective tissue.

We were able to obtain some evidence that in rheumatoid arthritis the metabolism of amino acids does not proceed normally, especially at the point of oxidative phosphorylation. The oxidation of substances of the tricarboxylic acid cycle, to which amino acids contribute, is retarded, because coupled phosphorylation in rheumatoid arthritis is too strict. This may account for an alteration in kind in the connective tissue, while it may mean just a quantitative change in the tissues generally.

I should also like to call attention to the work of Umbreit and Tonhazy (1949),* who have shown that only one amino acid (hydroxyproline) is under the direct control of cortisone at oxidation.

DR. MORRIS ZIFF (*New York, N.Y.*): When Neuberger, Perrone, and Slack (1951)† published their paper on the lack of turnover of collagen in rat-tail tendon, it was thought this might in part be due to the fact that the tail was just an avascular appendage, but now Dr. Kellgren has shown that liver and skin do not turn over either, and these are not avascular tissues.

I should like to ask Dr. Kellgren what he meant by procollagen, and the more soluble fractions of collagen.

At a discussion at a recent session of this society on the absence of hydroxyproline in fibrinoid it was suggested that fibrinoid is not of collagenous origin. Doubt was also raised that collagen was degraded significantly in "collagen disease". To-day the papers by Drs Sokoloff, Kulka, and Kellgren seem to point in this direction.

Like Dr. Clark, we have studied the excretion of hydroxyproline in patients with rheumatic diseases to get at the possibility of the breakdown of collagen in another way. As he did with phosphorus and nitrogen excretion, we have observed little difference between rheumatic and control subjects in the amount of hydroxyproline excreted, indicating perhaps again that breakdown of collagen does not occur to a significant extent in the rheumatic diseases.

CHAIRMAN: I should like to ask Dr. Kellgren if his method for isolating collagen was the Lowrey method, and whether it included reticulin?

DR. KELLGREN: In considering whether or not there is breakdown of collagen, I think we must think in terms of time relationships. It is true that the active rheumatoid perhaps loses 2 or 3 stones over a period of months, but there is not the slightest doubt that the vast majority of that weight loss is not due to loss of collagen, because it is total body wasting. On the other hand, there is some-

* Umbreit, W. W., and Tonhazy, N. E. (1949). *J. Bact.*, **58**, 769.

† Neuberger, A., Perrone, J. C., and Slack, H. G. B. (1951). *Biochem. J.*, **49**, 199.

thing peculiar about the rheumatoid patient if you look at him simply at the clinical level. It is, after all, his joints and his bones and his tendons and the dermis of his skin which tend to disappear—more so than in patients who waste from other diseases. So that over a period of years there would appear to be some loss of the collagenous structures; but it may not be possible to show this in metabolic studies in man.

There is no real evidence of a primary dissolution of collagen, and I am not going to defend that thesis. I am only throwing out an idea which may or may not be usefully followed up.

We have not as yet done starvation experiments to see whether they will alter the collagen turnover in the rats, and I think that is an experiment which should be made.

The so-called procollagen fractions are those which can be extracted from tissues by phosphate and citrate buffers. This work was done at the National Institute of Medical Research, and part of it has already been published in the *Biochemical Journal*.

Whether hydroxyproline is excreted in the urine is another question. Hydroxyproline may be metabolized or perhaps the kidney does not let it out. In our initial studies, the soluble proteins were extracted with 20 per cent. urea. The fibrous residue contains small quantities of elastin, but this is left behind in the second stage when the collagen is converted to gelatin by boiling.

Determination of C-reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever. By GENE H. STOLLERMAN, SAMUEL GLICK, and DALI J. PATEL, *Irvington-on-Hudson, N.Y.*

The behaviour of C-reactive protein (CRP) in the sera of sixty patients with acute rheumatic fever who were treated with cortisone, ACTH, and salicylates was studied. The CRP determination was found to be one of the most sensitive and reliable laboratory tests available for the detection of rheumatic activity and as a guide to the treatment and management of patients with rheumatic fever. A positive test for CRP is always associated with acute inflammatory disease and is presumptive evidence of rheumatic activity in the absence of other demonstrable causes of inflammation. However, "pure" chorea, erythema marginatum, subcutaneous nodules, and auricular myocardial Aschoff nodules may occur as isolated manifestations of the rheumatic process in the absence of a positive test for CRP. In addition, the test for CRP may be negative between cycles of rheumatic activity, and in the interval between a streptococcal infection and the onset of a rheumatic attack.

Reversal of a positive CRP to negative was found to be a helpful guide to evaluating the relative efficiency of the suppressive effect of cortisone and salicylates on the rheumatic process. Experiments have been done which lend support to the clinical impression that cortisone and ACTH do not suppress CRP directly (in contrast to the ESR), but more likely accomplish its reversal secondarily through suppression of the inflammatory state.

The CRP and the erythrocyte sedimentation rate (ESR) usually behave in parallel fashion. In the presence of congestive heart failure, however, the ESR may fall to normal values, whereas the CRP is not reversed. Conversely, disappearance of CRP from the serum usually indicates subsidence of the acute inflammatory process even though the ESR may remain elevated for prolonged periods.

Discussion.—DR. E. E. FISCHEL (*New York, N.Y.*): There are about a dozen tests for rheumatic activity, or rather for non-specific inflammatory activity which may be positive in a variety of inflammatory states, not necessarily bacterial or postbacterial. At one time or another in the course of inflammatory reaction, several of these tests may be somewhat more sensitive than others.

We have been studying four such tests simultaneously, two types of sedimentation rate (Westergren; Wintrobe; C-reactive protein, through the generosity of Drs Wood and McCarty; and serum complement), and we are finding decided variability at different stages of the disease. For general purposes, the crude sedimentation rate is still the most feasible test, and in some instances of rebound, of myocardial infarction, or of other inflammatory conditions, a change in sedimentation rate may be detected before the occurrence of C-reactive protein.

We have been concerned about the misinterpretation of the effect of hormones on these tests. The hormone affects, primarily, the inflammatory reaction and not the sedimentation rate indirectly, as has been implied. All the tests for inflammatory response are suppressed by hormone through suppression of the inflammation. A considered interpretation of this should not detract from the use and importance of these tests. Non-specific as they are for the diagnosis of rheumatic fever, they are specific for the presence of inflammatory reaction.

DR. GLICK: Cortisone may depress an elevated sedimentation rate because of its ability to diminish plasma concentrations of globulin and fibrinogen. We have been administering intravenous typhoid vaccine to a group of patients with Sydenham's chorea, and we find that along with the febrile reaction such patients manifest an elevated sedimentation rate and a positive test for C-reactive protein. If these patients are treated with cortisone or ACTH before, during, and after the administration of typhoid vaccine, the erythrocyte sedimentation rate will frequently remain well within normal limits, but the appearance of C-reactive protein cannot be suppressed. This would suggest that in the presence of an inflammatory process treated with cortisone or ACTH, the disappearance of C-reactive protein from the patient's serum would reflect a subsidence of the underlying pathology rather than a change in the metabolic processes concerned with the formation of C-reactive protein.

Effect of Early Short-Term Hormone Therapy in Active Rheumatic Carditis. By MAY G. WILSON, HELEN N. HELPER, ROSE LUBSCHEZ, KATHARINE HAIN, and NATHAN EPSTEIN, *New York, N.Y.*

Active rheumatic carditis is a self-limiting process. The cardiac damage sustained in any one attack depends on the duration and severity of the inflammatory process. It was therefore considered that if the acute inflammatory phase of active rheumatic carditis could be terminated by the use of hormone therapy before irreversible damage occurred, permanent cardiac damage might be prevented or minimized. This would obviously require therapy as early as possible after the onset of demonstrable active carditis. Because the duration of active carditis is variable,

an evaluation of the effect of ACTH or cortisone would be simplified by restricting the treatment to a short period. This report presents the results of administering ACTH and cortisone for an average period of 7 days in 33 patients during forty attacks of rheumatic fever.

Early administration of sufficient hormone therapy resulted in the arrest of progressive symptoms and signs of active carditis during the week of therapy. In the majority of patients there was termination of the attack with reversal of chamber enlargement and a return of the normal cardiac reserve without overt clinical evidence of increased cardiac damage. Recurrences were infrequent. Patients were ambulatory 2-3 weeks following onset and have so far maintained their cardiac status 6 months to 3 years since therapy.

It is concluded that early administration of short-term hormone therapy favourably alters the natural course of active carditis by arresting the inflammatory process before irreversible cardiac damage has occurred.

Observations on ACTH and Cortisone Therapy in Rheumatic Carditis. By ANN G. KUTTNER and JANET S. BALDWIN, *New York, N.Y.*

It is now established that the acute symptoms of rheumatic fever (polyarthritis, fever, and "toxicity") usually respond promptly to ACTH or cortisone. At the present time, however, two important questions remain unanswered:

(1) do these hormones actually terminate the rheumatic process, or is the improvement in the joint manifestations and in the general condition of the patient due to the suppression of the inflammatory reaction evoked by the rheumatic agent?
(2) is the ultimate scarring of the myocardium and the cardiac valves decreased by suppressing the inflammatory response, or does the rheumatic stimulus continue to cause tissue damage until it subsides in the natural course of the disease, even if the oedema and cellular reaction is inhibited?

It will be years before the second question can be definitely answered.

In an attempt to answer the first question ten children developing unequivocal clinical signs of carditis within 2 weeks or less of the onset of their first attack of rheumatic fever were treated with ACTH or cortisone. Therapy was given for a minimum of 3 and a maximum of 8 weeks. Three children received ACTH, two were given ACTH and cortisone, and five received cortisone.

At the present time seven of these ten children are considered to have organic heart disease. Hormone therapy did not uniformly prevent cardiac damage in patients with carditis treated within 2 weeks or less of the onset of their first rheumatic attack.

Cortisone Therapy in Initial Attacks of Rheumatic Carditis. By LAWRENCE GREENMAN, F. A. WEIGAND, and T. S. DANOWSKI, *Pittsburgh, Pa.*

Cortisone was given to 48 children, 3·9 to 15·4 years old, in their initial attack of rheumatic carditis, with diets rigidly limited in sodium and high in potassium, penicillin, and bed rest. The majority received cortisone orally for 8 weeks (300 mg. per day in divided doses for 6 weeks, and in decreasing amounts for another 2 weeks). Therapy was further prolonged if rheumatic activity persisted. All but four patients were observed for from 4 to 36 months.

Ten of twelve children treated within 2 weeks of onset now have normal hearts. Before therapy five had cardiac enlargement and congestive failure, one pericarditis, eleven mitral systolic, and two aortic diastolic murmurs.

Sixteen of the 23 treated between the 2nd and 6th weeks have normal hearts. At onset twelve had cardiac enlargement, eight congestive failure, three pericarditis, 22 mitral systolic, two mitral diastolic, and one aortic diastolic bruits.

Only one of the thirteen treated 6 weeks after onset now has a normal heart. Before therapy eleven had cardiac enlargement, seven congestive failure, two pericarditis, thirteen mitral systolic, three mitral diastolic, and three aortic diastolic murmurs.

Murmurs disappeared within 2 weeks in 11 per cent. of those who developed normal hearts, and within 7 weeks in 85 per cent. Reactivation occurred in two patients treated for 56 days, and in three treated for a lesser time. Cardiac enlargement impaired prognosis.

The data indicate that cortisone in adequate amounts under the regimen employed may prevent cardiac abnormalities in patients without previous heart damage if it is given within 6, and especially within 2, weeks of onset.

Discussion.—DR. B. F. MASSELL (*Boston, Mass.*): These three papers illustrate the fact that to-day there is still no unanimity of opinion regarding the value of cortisone and ACTH in the treatment of rheumatic fever. It is also apparent that there is no agreement regarding optimum dosage and length of treatment with hormones.

Some of the differences in the results of therapy reported this morning may be related to variations in criteria accepted by the investigators for active rheumatic fever and for cardiac involvement, and to variations in severity of the rheumatic process in the patients observed in the three medical centres—but it is also quite possible that the results are related to the variations in hormone dosage and duration of treatment.

Fundamental to the problem of the therapeutic value of the hormones is the degree to which these hormones are capable of suppressing the rheumatic inflammatory process in the heart. Since it is often very difficult to observe the changes which are taking place in the heart, we at the House of the Good Samaritan are conducting a study of the effect of ACTH and cortisone on the clinical course of subcutaneous nodules.

Nodules were selected for the study because in our experience 95 per cent. of patients with nodules develop rheumatic valvular disease, and because the microscopic architecture of the nodule is very similar to that of the rheumatic inflammatory lesions in the heart.

If the course of the nodules can be accepted as an indication of what is happening to the rheumatic inflammatory process, then it must be concluded that cortisone and ACTH can suppress this process to a high degree.

It further follows that if the inflammatory process can be suppressed in that way early in an attack of rheumatic fever and can be suppressed until the attack is over, then hormone therapy properly administered should be useful for preventing or reducing the amount of permanent heart damage that can result from rheumatic fever.

These considerations are consistent with the obser-

vations by Dr. Greenman and his associates that heart damage can be prevented by early hormone treatment of rheumatic fever and by the use of sufficiently large doses of the hormones over a sufficiently long period.

Dosage, duration of treatment, and the need for early treatment are all important questions. Promptness in beginning treatment may well be a matter not of weeks but of days. To waiting until signs of a significant degree of carditis are present before beginning therapy is in my opinion comparable to shutting the barndoor after the horse has run away.

DR. EDWARD E. FISCHEL (*New York, N.Y.*): The very diversity of these three papers is evidence that little can be stated categorically about striking beneficial results. None of them included a control series. By control, I do not mean experience in the literature or experience in the past at the same institution, but randomly selected or alternating cases.

In our own experience, and I know in that of Dr. Kuttner, Dr. Massell, and several other investigators, a randomly selected series of patients treated with salicylate or with the two hormone preparations were observed. No striking difference was seen among the three treatment groups when a large variety of signs and symptoms and all the usual criteria of rheumatic fever are followed. A preliminary report of the Co-operative Study on Rheumatic Fever was presented to this Society last year with substantially this result. There are, of course, further tabulations in progress.

It should be stated that treatment failures and even deaths have occurred with hormones, as they have with salicylates, as might be expected in a disease as variable as rheumatic fever. It is obvious that maximum illness cannot be treated. After all, treatment failures have been observed with pneumococcus pneumonia treated with penicillin, and I think no one will say that either salicylates or the hormones are as specific for rheumatic fever as penicillin for pneumonia. Nevertheless, certain axiomatic conclusions are to be noted. These are that early treatment, uninterrupted treatment, and prolonged treatment, with any of these agents may be decidedly beneficial in most instances.

We agree that treatment directed against the inflammatory process is highly desirable in acute rheumatic fever, but we perhaps disagree as to the signs and symptoms of rheumatic inflammation. There is no reason to suppose that rheumatic fever in the heart is qualitatively different from other aspects of the disease from the pathogenetic point of view. Heart inflammation may be of a more subtle type than that expressed by cardiac dilatation or murmurs, and may be reflected merely by a rise in temperature and sedimentation rate in the absence of foci of clinical inflammation. These are factors to consider in judging a clinical response. The presence of polyarthritis and other abnormalities which follow a streptococcal infection may suggest that cardiac inflammation is also present, and microscopic observation would probably reveal it. Several studies have shown that we cannot diagnose rheumatic activity in many patients who subsequently show up with rheumatic heart disease, partly because they never seek a doctor's help. Any arbitrary definition of signs necessary to the diagnosis does not allow for the total number of people who probably have rheumatic fever.

The use of fluoroscopy as a diagnostic tool as well as a criterion of improvement presents some difficulties. Chest fluoroscopy is difficult to standardize and reproduce. We know nothing of the variations due to body build, or of changes due to febrile states such as occur even in simple pharyngitis which may cause some degree of cardiac dilatation. Dr. Wilson's efforts in the determination of ranges of variation are to be encouraged, but one method must not supplant others. If clinical improvement is to be measured, the methods must correspond to the accepted clinical picture, or perhaps exceed the duration of patent clinical evidences of rheumatic inflammation.

Similarly, the measurement of vital capacity presents problems of training, adaptation, and incentive, as well as variations with fatigue, malaise, fever, bed rest, and body build. It is not solely a reflection of cardiac function, and ranges for normal and abnormal are not well defined, particularly in children.

With regard to the short-term hormone treatment, several patients referred to the Presbyterian or Babies Hospitals, after cessation of 7 to 10 days of treatment with hormones, had serious rebounds of rheumatic activity. In a few instances the subsequent flare-up exceeded the severity of the presenting picture. In two instances, where large doses of hormone and salicylate were given, friction rubs persisted for from 10 days to 3 weeks, and both patients subsequently died. Evidences of continued rheumatic inflammation after treatment, such as a continued elevation of sedimentation rate or temperature in a person who is a known rheumatic and has no other illness should not be disregarded.

Relative to large doses of cortisone, Dr. Greenman's results do not differ from well-treated salicylate cases where early, adequate, and prolonged treatment has been instituted. I re-emphasize that early treatment is axiomatic.

The toxicity of cortisone may be outside the realm of mere salt-and-water retention or penicillin-sensitive infection which Dr. Greenman tried to prevent. As Dr. Kuttner indicated, hypertension may occur. There are also such complications as perforated viscera, thromboses, and non-penicillin-sensitive infections which cannot be prevented in long-term, high-dosage cortisone therapy.

We have seen decided benefit from one or other of the antirheumatic agents at various times, and in severe cases we are tending to employ a combination of long-term salicylate with cortisone and corticotrophin as an adjunct for the early suppression of inflammation. In such instances we have been impressed by the apparent ability of continued administration of salicylate to diminish the severity of the expected rebound when the hormones are stopped.

DR. CURRIER MCEWEN (*New York, N.Y.*): I should like to comment on one of Dr. Greenman's remarks: that is that the patient who had been ill longer fared less well than those who had been treated within 2 weeks of illness. He very properly pointed out that conclusions should not be drawn from a long series of cases including patients with illness of varying duration. But the ten patients reported by Dr. Kuttner all were treated within 2 weeks of onset of illness; so they are in that sense comparable to Dr. Greenman's group of twelve patients.

In Dr. Kuttner's series the majority of those patients were considered to have some evidence of organic heart disease at the end of the treatment period and during the follow-up phase. To be sure, six of those ten patients were not treated according to the same regimen as Dr. Greenman's, but, on the other hand, four were so treated. Of those four, two apparently ended up with undamaged hearts, and two did not, a result that might

have been expected with any form of therapy or with none.

I wonder whether part of the difference may not be due to differences in the criteria of organic heart disease. Perhaps some patients considered by Dr. Kuttner to have organic heart disease, as shown by slight enlargement or mitral valve insufficiency, might have been considered by others to have normal hearts. That is a hazard that cannot be overcome with our present means of measurement, but it has to be taken into account.

Like Dr. Massell, I was impressed by what happens to subcutaneous nodules. It seems reasonable to accept this as indirect evidence of what may be going on in the myocardium. One likes to hope that that is the case, for any agent that can give any hope at all of suppressing the inflammatory reaction in the myocardium is worth using, in spite of conflicting evidence.

DR. WILLIAM R. MERCHANT (*Washington, D.C.*): What was the duration of disease in the patients in Dr. Wilson's group, and was her previous experience of salicylate for a similar period?

DR. RUSSELL L. CECIL (*New York, N.Y.*): I agree with what Dr. McEwen has just said. It seems to me that this is ultimately a question of cellular pathology. I like Dr. Massell's study of the nodules showing that these cellular reactions disappear under the effect of cortisone. We cannot settle this problem until we have had a long-range study of these lesions, what happens to them after the patient has recovered, a year or two after the acute attack.

All of us who are in practice are faced with the problem of a child in his first attack of rheumatic fever. My own feeling would be that, in view of the evidence which has been presented, a child in his first attack of rheumatic fever should have the benefit of cortisone therapy.

CHAIRMAN: I should like to ask Dr. Massell whether the controlled nodules were completely controlled, or whether the patients were on long-term salicylate?

If we start dealing with the treatment of initial attacks early, we are going to include many patients who would have recovered by themselves. It is the same problem that comes up when you start treating any early disease, and it is a difficult one to solve.

DR. WILSON: After too many years of following patients with rheumatic heart disease, I find it very difficult to understand why there is any question as to the value of hormone therapy in active carditis.

To answer the specific question, in my file of over 1,500 patients who had *bona fide* rheumatic fever and rheumatic carditis during their childhood, there is not a single patient with a normal heart according to the criteria of the Heart Association (requiring, in addition to murmurs, cardiac chamber enlargement). Many of these patients were on salicylate therapy. Only in the last 3 years since the advent of hormone therapy have I had patients with rheumatic fever and active rheumatic carditis, diagnosed clinically and confirmed by fluoroscopic examination, who have now no evidence of heart enlargement. These patients were out of hospital by the 3rd week, and returned to school and remained perfectly well, although in some non-specific laboratory evidence, such as a rapid sedimentation rate, persisted for some time.

I think that Dr. Fischel indicated that the additional diagnostic criteria of active carditis, besides the routine clinical physical examination, were questionable. Over the past 15 years we have used routine fluoroscopy in the posterior/anterior and oblique views on children observed from birth: 500 to be exact. We found the incidence of variations in normal children to be 10 per cent., observed in 2,973 serial fluoroscopic examinations by 35 different examiners, an average of five examiners per patient.

Two of the staff reviewed the cardiac charts of one hundred patients and found that again, in 1,393 serial fluoroscopic examinations done since 1932, sporadic variations due to technique or posture occurred in less than 10 per cent. The use of more exact criteria to detect cardiac chamber enlargement which may not be found on physical examination or the posterior/anterior view should not detract from the value of such criteria.

DR. GREENMAN: I should like to add several comments that I think are pertinent to the evaluation of our data. In addition to the criteria previously mentioned, the patients were followed by observation of temperature, pulse, blood count, sedimentation rate, and serum fractional protein. All findings were normal and remained so after cessation of cortisone before a patient was considered well. The serum proteins have served as a more useful index of activity of rheumatic fever than the sedimentation rate since they were slower to return to normal. However, no test proved completely reliable for predicting inactivity of this illness while the patients received cortisone.

Multiple observers assessed the cardiac status of our children. No youngster was considered normal after treatment if any murmur or other cardiac abnormality was detected.

Only patients with definite carditis before therapy were included in this series. If a systolic apical murmur was the only evidence for carditis, it had to be Grade II or more and transmitted towards or into the left axilla to be considered significant.

I regret that Dr. Kuttner's data and ours are not comparable, since she used compound F instead of cortisone, although the amount administered was similar in four of her patients. That may explain her high incidence of undesirable side-effects in contrast to our experience, since the two hormones are not identical.

DR. MASSELL: In answer to Dr. Ragan's question, the patients who had the few and multiple nodules that took so long to go away either received no treatment except bed rest or were on salicylate, in doses large enough to cause symptomatic relief. I didn't have time to mention the fact that many of these cases who developed nodules in the non-hormone treated group, in fact some who were included later in the hormone-treated group, actually developed nodules while on salicylate. It is our conclusion that salicylates do not influence the course of nodules, whereas the hormones do so.

Reactivation of Rheumatic Fever following Mitral Commissurotomy. By LOUIS A. SOLOFF, JACOB ZETUCHNI, O. HENRY JANTON, THOMAS J. E. O'NEILL, and ROBERT P. GLOVER, *Philadelphia, Pa.*

Of 180 consecutive individuals who were regarded as having clinically inactive rheumatic fever and who had mitral commissurotomies, 68 developed within 2 to 8 weeks after operation, pain dissimilar in character and in location from the post-operative incisural pain. Of these 68, 44 were recognized to have fever. These 44 individuals are the basis of this report.

The pain is variable in intensity, location, and distribution and simulates that seen in pericarditis. Fever averages 100° to 102° F.; it frequently outlasts pain and is present for 10 days to 4 weeks. After an asymptomatic interval of 2 to 4 weeks, the entire symptom-complex may repeat itself. Our patients averaged two to three cycles, but some had six or seven and one had fourteen. In no instance was an independent illness or infection uncovered. Laboratory studies were non-specific. Roentgenological studies revealed an increase in the cardiac silhouette compared with the pre-operative picture and at times a pleural reaction. Electrocardiographic studies revealed changes suggestive of increased myocardial abnormalities, pericarditis, or both.

These 44 individuals with pain and fever sub-divided into eight groups according to the associated clinical findings:

(1) five with fever and pain only,
(2) four with psychosis,
(3) thirteen with heart failure,
(4) twelve with arrhythmias and heart failure,
(5) three with migratory arthritis and heart failure,
(6) two with arrhythmias, migratory arthritis, and heart failure,
(7) two with haemoptysis and heart failure,
(8) three with heart failure terminating fatally.

The prognosis is variable but is compatible even in those with prolonged morbidity with an ultimate improvement in myocardial function compared to the pre-operative state (as determined by an eighteen-month follow-up period).

Because this syndrome has not been recognized by us after any other type of cardiac or pulmonary surgery, because of a lack of evidence of an independent illness or infection, because of the delayed onset and cyclic character of this syndrome and because of associated major abnormal cardiac phenomena, we regard it as a reactivation of rheumatic fever.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): Dr. Soloff reports that about 40 per cent. of the biopsies of the auricular appendages showed positive Aschoff bodies. The figure is consistent with that reported by others. I wondered whether there was any correlation in the incidence of these positive biopsies with the occurrence of the clinical syndrome post-operatively.

DR. E. F. TRAUT (*Chicago, Ill.*): I should like to have Dr. Ragan comment upon the post-operative use of hormones inasmuch as some proliferation of the deep tissues is necessary and desirable in the healing of the cardiac defect due to operation.

I am always uncertain whether I should use those hormones in patients who have had operations, particularly those involving the viscera.

CHAIRMAN: To block the reparative process completely you need practically a lethal dose of hormone. In man the usual dose of hormone causes delay in the appearance of repair. We have been loathe to use massive doses of hormone during visceral surgery, but otherwise we have relatively little hesitation in continuing it.

We have no experience with hormone therapy during commissurotomy operation.

DR. CURRIER MCEWEN (*New York, N.Y.*): Is there any information about the antistreptolysin titre in these patients before and after the appearance of the post-commissurotomy febrile syndrome.

DR. CHARLES M. PLOTZ (*Brooklyn, N.Y.*): There is a group in our laboratory at Mount Sinai Hospital, headed by Dr. Elster, that is studying the antistreptolysin test and C-reactive protein reaction in the post-commissurotomy syndrome. The number of cases is still too small, but preliminary data would seem to indicate that during the syndrome the C-protein may be elevated in the presence of normal antistreptolysin titre. This, of course, is what might be expected in an inflammatory reaction not necessarily associated with previous infection with the beta-haemolytic streptococcus.

DR. SOLOFF: In answer to Dr. Bunim's question, we found no correlation between biopsy of the left auricular appendage positive for Aschoff bodies and the post-operative syndrome which we regard as a re-activation of rheumatic fever. Our incidence of positive biopsies in patients with the syndrome was 40·5 per cent., an incidence similar to that found in patients who do not develop it.

The biopsy obviously represents but a small fraction of the entire heart. In two individuals who unfortunately died after operation, Aschoff bodies were found in the ventricular muscle, although the pre-operative biopsy of the auricular appendage was negative for Aschoff bodies. We share the pathologists' opinion that the incidence of Aschoff bodies varies in different regions of the heart and is greater in the ventricular portions of the heart than in the auricular.

We agree with Dr. Ragan about the use of hormones, preferring not to use them unless the patient is extremely sick or has prolonged severe pain. We have used cortisone and ACTH for these reasons and have seen symptomatic improvement.

We have turned over the problem of antistreptolysin and antihyaluronidase titres to Dr. Harris at the Children's Hospital in Philadelphia, and yet, no definite conclusions have been reached.

I can say, however, that in two individuals who developed an immediate post-operative unmasking of active rheumatic fever, as evidenced both by clinical symptoms and by prolongation of the PR interval, that the titres did not rise. Their titres, before and after operation, were regarded by Dr. Harris as falling in the intermediate or doubtful zone.

We have asked Dr. Harris whether these tests are significant for an apparently mechanical method of activating rheumatic fever, in contrast to the natural method of activation in which there is a preceding streptococcal infection. I was interested to hear one of the discussants say that following mitral commissurotomy, the C-reactive protein was elevated, but the antistreptolysin titre was not, for that is what I should have expected. The sedimentation rate was always elevated.

Physiology of Articular Blood and Nerve Supply. By ERNEST GARDNER, *Detroit, Michigan.*

Synovial tissue is primarily responsible for the production of a viscous, lubricating fluid, the formation of which is largely dependent upon the blood flowing through

synovial tissue. This is a connective tissue, composed of formed elements such as cells and fibres, together with matrix or ground substance. One of its most characteristic morphological features is a capillary network adjacent to the joint cavity. This capillary network is derived from blood vessels which also supply the capsule and neighbouring epiphyses. In addition, there are arterioles with heavy coats of longitudinal muscle. These are found in the capsule and seem to be arteriovenous anastomoses; they are important in regulating the flow of blood.

Joints are supplied by nerves which though they may vary considerably in the manner in which they reach a joint, may, nevertheless, supply a constant region of a joint, any major region of a joint receiving branches from at least two different articular nerves. The fibres in these nerves form the following endings, which subserve a variety of functions:

(1) Ruffinitype endings in the joint capsule, concerned with proprioceptive functions.
(2) Free nerve endings in the joint capsule and in vessel adventitia, concerned with pain.
(3) Simple endings in vessel adventitia concerned with unknown vasosensory functions.
(4) Free endings or smooth muscle or vessels, concerned with vasomotor functions.

Discussion.—DR. J. H. KELLGREN (*Manchester, England*): We have never seen anything like this beautiful presentation of anatomical and physiological studies before in this field. Dr. Gardner has made two rather important points which have a considerable practical application: first is the degree of sensitivity of the capsule as opposed to the synovial membrane in joints; and, secondly, the great variety of reflex disturbances that may result from the stimulation of pain fibres.

DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa.*): If more work is carried out on the lines of this clear summary of the vascular and neurological aspects of joint function, we shall soon understand many of the now obscure clinical pictures—reflex dystrophy and the rest of them—that have puzzled us for so long.

CHAIRMAN: We have been extremely fortunate in our choice of invited guests at this meeting. I used the word elegant to describe Dr. Kellgren's paper and I don't want to be repetitive, but I think it applies to this paper as well. I have an extensive reprint file of Dr. Gardner's individual studies, but I wonder if he has ever put this material into one paper.

DR. GARDNER: I did a review in *Physiological Reviews* a few years ago, but we have assembled a lot of material since then; most of it has appeared in individual publications, or is not yet published.

Aminotripeptidase Content of the Synovial Fluid of Patients with Arthritic Diseases. By MORRIS ZIFF, JEROME SIMSON, EDWARD SCULL, *New York, N.Y.* and JOSEPH J. BUNIM, *Bethesda, Md.*

The extent of synovial inflammation is usually judged by the leucocyte content of the synovial fluid, but this is often rendered inaccurate by the presence of particulate matter.

If an inflammatory reaction is present in the lining membrane of a body cavity which contains fluid, the dissolution of cells in the membrane should release into the fluid the enzyme contained in these cells. The amounts of enzyme released may be expected to be proportional to the extent of inflammation.

The enzyme aminotripeptidase has been shown to be widely distributed in tissues and to be richly concentrated in leucocytes. It is a stable enzyme and is determined by measuring the rate of hydrolysis of a tripeptide, of which glycylglycylglycine is an example.

Aminotripeptidase was determined in 111 samples of synovial fluid obtained from 103 patients with a variety of arthritic diseases, including rheumatic fever, rheumatoid arthritis, degenerative joint disease, gout, gonococcal arthritis, and a group of miscellaneous diseases. In degenerative joint disease, and in rheumatic fever, the aminotripeptidase activities were low and essentially of the same magnitude as found in the serum. Relatively low values were recorded in the miscellaneous arthritides. The highest activities were noted in rheumatoid arthritis where the mean activity of the synovial fluid was about five times greater than that of the serum. In gout, the range of values was wide. The aminotripeptidase content was not directly related to the leucocyte count of the synovial fluid.

Discussion.—DR. CURRIER MCEWEN (*New York, N.Y.*): One can make many observations on synovial fluid indicative of an acute inflammatory process in the joint. The evidence thus far suggests, however, that in the aminotripeptidase reaction information can be gained regarding the synovial membrane itself.

DR. MARION W. ROPES (*Boston, Mass.*): I am interested in the differences seen between rheumatoid and the other diseases because they indicate that the change is not merely associated with inflammation in general, but to the *type* of inflammation. Particularly interesting were the findings in streptococcal arthritis. If those fluids had positive cultures, I think it is surprising that they had such a low content of the enzyme in contrast to the other diseases in which a comparable degree of inflammation is present. The same might be said of gout.

The low level in lupus fluids is interesting, and I wonder whether this finding might not be an even more reliable differential diagnostic test for lupus erythematosus versus rheumatoid arthritis than the finding of L.E. cells, as in the one patient classified in the lupus group, in whom the fluid enzyme content was very high.

DR. JOHN LANSBURY (*Philadelphia, Pa.*): Is this method sufficiently simple to be used in follow-ups in the average clinic?

DR. ZIFF: When cells die, the enzymes contained in the cells of the synovial membrane are liberated. Since there is no relationship between the cellularity of the fluid itself and aminotripeptidase content, the latter must represent changes going on in the synovial tissue.

The patients with streptococcal and gonococcal arthritis did not have positive synovial fluid cultures. I think there would be much more tissue destruction and that the value would be higher in the presence of a positive culture.

The patient with lupus erythematosus could easily have been considered to have rheumatoid arthritis if he had not had haematuria and a positive "L.E." test.

As far as the simplicity of the test is concerned, if the clinic has a technician who knows how to titrate, the test can be done.

Dynamics of Radioactive Cortisone Distribution in Rheumatoid Arthritis. By T. F. GALLAGHER (by invitation), LEON NELLMAN (by invitation), H. L. BRADLOW (by invitation), JACK ZUCKNER, and RICHARD FREYBERG, *New York, N.Y.*

Radioactive cortisone was administered intra-articularly to a patient with rheumatoid arthritis with a large joint effusion. At intervals, samples of synovial fluid, blood, and urine were obtained, and the concentration of the hormone and its metabolites were determined by radioactivity measurements. The rate of disappearance of cortisone from the joint and the accumulation in the other body fluids were calculated from these data. After a suitable interval, radioactive cortisone was administered intravenously to the same subject and the accumulation of radioactivity in the blood, urine, and joint effusion was again measured. Subsequently, the accumulation and disappearance of radioactive sodium in joint and body fluids were followed in the same patient in parallel fashion with the procedure described for cortisone. Comparison of the cortisone data with the radioactive sodium determinations indicated that similar mechanisms of distribution were involved with both substances.

Discussion.—DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa.*): This work leaves no room for question as to its validity. It represents a milestone in arthritis research. However, we have reason to believe that intra-articular *hydrocortisone* would not behave in exactly the same way as cortisone, and I wish to present quickly some findings that show a marked difference in the fate of the two hormones when injected intra-articularly:

(1) There was no significant difference in the disappearance rate of cortisone acetate or hydrocortisone acetate in 26 instances after simultaneous injection of equal amounts into contralateral joints. Both hormones disappeared almost completely in 2 hrs after the time of introduction, determined by the Porter-Silber reaction.

(2) In the 26 cases the synovial fluid was centrifuged, and the cells were washed and macerated by ultrasonic vibration for steroid extraction. The concentration of hydrocortisone were more than double those of cortisone, and they remained elevated for longer periods.

(3) Chromatographically it was determined that the steroid in the *cells* of the synovial fluid consisted of unchanged acetylated compound E or F, whereas the supernatant synovial fluid showed a rapid proportional increase of the free alcohols and tetrahydro compounds of E or F. This indicates a fairly rapid hydrolysis of each hormone in the synovial fluid, but much slower change in the *cells* of the synovial fluid.

(4) Our latest work is most significant here. We injected 25 mg. cortisone acetate or hydrocortisone acetate into five arthritic knee joints at various intervals prior to synovectomy. At operation, the excised synovial tissue was immediately transferred to the endocrine laboratory, where it was washed, and the inner layer dissected free. The lining layer of synovial tissue was then macerated and extracted for steroid analysis both by the Porter-Silber reaction and by paper chromatography. Our preliminary results show that a large proportion of the intra-articularly injected F acetate is taken up and apparently stored by the lining cells of the synovial membrane in concentrations of 120-150 μg./g. of synovial lining tissue, and remains at least for some days, whereas less than half the amount* of E acetate is absorbed, and disappears much more quickly from the synovial lining. We think this difference provides a clue to the reason for the greater local effectiveness of hydrocortisone in the arthritic joint. We shall be interested to know what Dr. Gallagher and his co-workers find when they repeat their studies using intra-articular radioactive *hydrocortisone*.

DR. KARL MEYER (*New York, N.Y.*): This comparison between the disappearance of sodium ion and that of cortisone may be somewhat misleading. The rate of disappearance may simply measure the slowest possible reaction of diffusion through a highly viscous material, so that neither the electric charge nor the molecular diameter nor the solubility characteristic of the material diffusing out makes any difference. Has Dr. Gallagher carried out any experiments by lowering viscosity with hyaluronidase, for example, and then measuring disappearance rate.

DR. MORRIS ZIFF (*New York, N.Y.*): This application of the combined techniques of isotope and steroid chemistry to the problem of steroid metabolism in the synovial cavity and of the diffusion of cortisone through the synovial membrane and back again is truly impressive.

Dr. Glyn, Dr. Scull, and I have been studying the disappearance and metabolism of cortisone and hydrocortisone in the synovial cavity in collaboration with Dr. Hildegard Wilson, in whose laboratory all steroid analyses have been done.

At 5 to 60 minutes after injection of hydrocortisone, the synovial fluid was aspirated and the synovial cavity washed with saline. By Porter-Silber assays on the crude extracts, we got back 28·2 mg. out of 50 mg. (or 56 per cent.) after 5 minutes. After half an hour we obtained 4·4 mg. (about 9 per cent.), and finally, after an hour, we recovered no Porter-Silber assaying material, although something did show up on chromatography.

The patient had been given 100 mg. cortisone per day orally for close on 3 years.

When control synovial fluid was assayed, cortisone was not found, but we did find a tiny amount of a steroid with the mobility of Compound F, rather than cortisone.

The fluids, when chromatographed, showed mainly the Compound F which had been injected, but there is evidence of metabolites moving slower than hydrocortisone, and on the 5-hour papers, which are faster, we found evidence of several metabolites which move faster than hydrocortisone. The slow and fast metabolites were eluted from the paper, combined separately, and rechromatographed for the same periods of time.

In the control fluid, the slow paper (7 days) showed evidence of a metabolite with the mobility of a tetrahydro compound which could be tetrahydrocortisone. The intermediate paper gave evidence of a metabolite with a mobility similar to that of cortisone. On the rapid paper we found a metabolite with the mobility of corticosterone. It might not have been the same, but it had a similar mobility.

* We have obtained no higher value than 50 μg./g. of tissue, and that was only 3 hours after injection.

Our experiments have demonstrated:

(1) the absence of cortisone in the synovial fluid of several patients receiving cortisone orally. In one, we found a small amount of a compound with the mobility of hydrocortisone, and in the other, a small amount of a compound moving like tetrahydro E or F.

(2) the rapid disappearance of cortisone and hydrocortisone after intra-articular administration.

40 per cent. gone in 5 min.
85 per cent. gone in 60 min.
98 per cent. gone in 180 min.

(3) the appearance of well-localized bands which were not seen in either the control synovial fluid or the suspension which was injected. These are taken as evidence that chemical transformation of the injected steroid had been effected, either by the synovial tissue or by the inflammatory cells infiltrating the synovial membrane.

DR. GALLAGHER: Drs Hollander and Ziff have made very interesting additions to our report. We hope eventually, when we have completed a successful synthesis of hydrocortisone, to study the problems raised by them.

In answer to Dr. Meyer's question, we have done no experiments other than those now reported.

Effects of Nitrogen Mustard Therapy in Patients with Rheumatoid Arthritis. By W. D. PAUL, R. E. HODGES, W. B. BEAN, J. I. ROUTH, and KATE DAUM, *Iowa City, Iowa.*

This is a preliminary metabolic study of ten individuals with rheumatoid arthritis who were given nitrogen mustard. The patients were observed over an 8-month period, during which time clinical, endocrine, and metabolic studies were carried out. The Steinbrocker classification was used to rate the severity and stage of arthritis. An arbitrary method of measuring joint mobility with a goniometer was devised. Erythrocyte sedimentation rate, complete blood counts, protein partitions by the electrophoretic method, glucose tolerance curves, eosinophils, plasma protein bound iodine, and 17-ketosteroids were obtained at intervals of approximately 2 months. Nitrogen, calcium, and phosphorus balances were studied.

During a control period of 4 months, the patients were treated with salicylates and physiotherapy only. A slight improvement of arthritis was noted. Nitrogen mustard was then given. The degree of improvement increased and was maintained during the next 4 months. There were no changes in the erythrocyte sedimentation rate and eosinophil counts, but slight alterations of plasma proteins toward normal and a transient fall of leucocytes occurred. There was no evidence of endocrine stimulation or suppression as a result of nitrogen mustard therapy. During the control period all patients exhibited positive phosphorus and negative nitrogen and calcium balance, despite an excellent diet supplemented with vitamins and minerals. The immediate effect of nitrogen mustard therapy was loss of appetite accompanied by heavy losses of nitrogen, calcium, and phosphorus. Within a week, improvement of appetite, and return to normal nitrogen, calcium and phosphorus balances occurred. Liver function, as estimated by the bromsulphalein test, was unaltered.

Discussion.—DR. ARTHUR LAWRENCE SCHERBEL (*Cleveland, Ohio*): We have used nitrogen mustard alone and in combination with various non-specific agents in sixty patients with active rheumatoid arthritis during the past 2 years. Nitrogen mustard is a potent vesicant which reacts with a variety of biologically active substances, and it is not known whether alteration in antigen-antibody mechanism is responsible for improvement in rheumatoid arthritis.

Fifteen patients received 0·1 mg./kg. nitrogen mustard on 4 consecutive or alternate days, which resulted in temporary improvement of inflammatory joint manifestations, but was associated with a high incidence of nausea, vomiting, muscle weakness, leucopenia, and decrease in haemoglobin.

The remainder of our patients received 1 to 2 mg. nitrogen mustard daily for 4 days, combined with 300 mg. isonicotinic acid hydrazide daily as continual maintenance therapy. Isonicotinic acid hydrazide has certain desirable features and is worthy of further investigation.

Our interest was directed toward electrophoretic protein patterns and non-glucosamine polysaccharides as described by Shetlar.

When nitrogen mustard was given, the alpha-globulin, serum polysaccharides, and erythrocyte sedimentation rate decreased, and the albumin component increased. These changes were usually of temporary duration.

Perhaps the most interesting observation in 120 patients followed serially with electrophoretic patterns was that various agents, including mustard, isonicotinic acid hydrazide, cortisone, ACTH, and gold, caused favourable improvement, if certain electrophoretic patterns existed before treatment; and actually response to therapy depended more upon the type of pattern existing before treatment than the drug used for treatment. Certain patterns resolved with greater rapidity and completeness than others, yet the complexity of the pattern did not always parallel the severity of the disease as reflected by joint involvement or duration of illness. We have, therefore, divided these patterns into groups inasmuch as variation in response to non-specific agents not infrequently paralleled the disease activity as reflected in the protein pattern.

DR. CURRIER MCEWEN (*New York, N.Y.*): Several years ago, Dr. Chasis, in our department of medicine, was using nitrogen mustard in the treatment of glomerular nephritis and suggested that we should try it on some patients with rheumatoid arthritis. We only treated two patients, and they were not studied with the care devoted to Dr. Paul's patients, but no clinical improvement of any kind, subjective or objective, was seen, and we did not think it worth while going on.

DR. JOHN GLYN (*New York, N.Y.*): Before I came to the U.S.A. a year ago, I was working in London in Dr. W. S. C. Copeman's Unit, and one of the members of the unit had returned from a visit to Spain full of enthusiasm for the nitrogen mustard therapy which he had witnessed in Dr. Jimenez Diaz's clinic in Madrid.

We accordingly set up a pilot therapeutic trial of our own, concentrating only on the clinical and haematological responses. We treated seven cases and were completely convinced that, in our hands at any rate, it did not produce objective improvement.

However, when Dr. Diaz visited us he was not dismayed by our lack of results, and told us that we were using too small dosage.

We therefore increased the dosage from 3-4 mg. a day

on 3 successive days to 6-8 mg. daily, and this regimen resulted in dramatic and frightening side-effects in all cases, with only one case of doubtful improvement, and we gave up the trial at this point.

DR. SUMNER Y. ANDELMAN (*Tulsa, Okla.*): We have used this drug in 6 patients. One had subjective improvement which lasted about 4 days; the other five became much worse, and about a month or two later we used cortisone. The patients who received cortisone made a dramatic improvement. One patient, who was subsequently proven to have periarteritis nodosa, went down hill rapidly 2 weeks after nitrogen mustard.

DR. PAUL: As Dr. Scherbel pointed out, this study was part of a metabolic study of rheumatoid arthritis and not primarily a clinical evaluation of nitrogen mustard. We have been attempting to discover any measurable change in rheumatoid arthritis that might occur when an anti-rheumatic drug is given or a new method of treatment is tried. In this way we would have some definite means of evaluating such a drug or technique. Only cases of proven rheumatoid arthritis were used in the study. The dose of nitrogen mustard was reduced so that the subjects were given only a total of 0·1 mg./kg., 0·05 mg./kg. for 2 consecutive days. Having treated many patients for Hodgkin's disease or bronchogenic carcinoma, etc., we found it advantageous to give the material at night, to have the patient well sedated, and to keep him in the prone position with the head hanging over the bed to allow secretions to drain. Using these precautions and observing the patients for the first 7 days we have seen no severe reactions. More recently the surgeons have even asked us to introduce nitrogen mustard into the aorta or other arteries during laparotomies.

Our patients state that they would rather have this form of therapy than many others which they had previously received. They also feel that the nitrogen mustard is of benefit. Finally, our primary interest was to discover any abnormality which might change after giving an anti-rheumatic drug. The suggestion of Dr. Scherbel to analyse the electrophoretic pattern of a patient before giving the drug is a good one.

Implantation of Placental Tissue in Patients with Rheumatoid Arthritis. A Preliminary Report. By ROBERT M. LINTZ, *New York, N.Y.*

European investigators have studied the effect on rheumatoid arthritis of the implantation of various tissues. In this study, human placenta was employed. The material was made sterile by saturation with 1 per cent. aqueous solution of brilliant green and was placed under the fat layer of the thigh. There were no unfavourable reactions to this procedure.

Thirty-five patients, twelve males and 23 females, varying in age from 22 years to 70 years were studied. The duration of the disease was from 3 months to 50 years. In four patients the disease was classified Stage II, in twenty Stage III, and in eleven Stage IV. The functional capacity was Class 2 in ten, Class 3 in eighteen, and Class 4 in seven. In all but two patients the erythrocyte sedimentation rate was elevated. After the course of treatment fifteen patients showed no improvement (Grade IV), four were Grade II, and sixteen were Grade II. There were no Grade I results.

The patients who improved experienced subjective improvement within a period of 2 to 10 days after the implant; objective improvement was manifested by decrease in heat, reduction in swelling, and increase in range of motion. Subjective and objective improvement were progressive for 2 to 6 weeks. The patients who improved have maintained their improvement to date; this includes two patients with improvement of 4 years' duration, two of 3½ years, and one of 3 years. The sedimentation rates did not return to normal but were generally lowered.

It is not believed that the placental implant had any hormonal effect and tissue specificity is doubtful. These preliminary studies are not reported as a new method of treatment but as a basis for further investigation.

Discussion.—DR. WILLIAM H. KAMMERER (*New York, N.Y.*): Thirteen of the patients presented were under the care of Dr. Cecil and myself, and we had followed them for a number of years. All had well established diseases, four being Stage II, eight Stage III, and one Stage IV. Eight out of the thirteen were in Class III. They had had the disease for a long period and had run the gamut of therapy from bee venom down to wearing copper bracelets and were ready to snatch at almost any straw.

Six of them seemed to derive substantial benefit, two having a quite striking improvement.

The improvement was manifested chiefly in improvement in functional capacity, which enabled them to move from Class III to Class II.

Objective improvement, as measured by the A.R.A. criteria, was less striking, and this is particularly true with regard to the sedimentation rate and sheep cell agglutination titre, which showed no significant alteration.

I did not feel that the rheumatoid activity was completely suppressed, and such figures as these have been reported for many agents in the past. Also, the follow-up period is relatively short.

I am always reminded when I embark on a trial of the newest "cure" for rheumatoid arthritis of an experience of Charlie Short's. A few years ago we were stimulated at an annual meeting by the proposition that testosterone, pregnenolone, and other so-called steroid hormones were capable of altering the course of rheumatoid arthritis. Charlie Short was sceptical, and set up an elaborate protocol to demonstrate it wasn't so. Unfortunately, the first patient that he treated reacted in the wrong way—had a marked and wonderful improvement. This was so discouraging to Charlie that he abandoned the experiment (*Laughter*).

Now, I am sure we have all had similar experiences. I believe it was Charlie or his group who coined the term "reactors" for a group of patients with rheumatoid arthritis who seemed to improve, regardless of what you did to them—slamming the door, cutting their hair, or giving them an injection of most anything. It is one of the things, of course, that makes the therapeutic evaluation of a new agent in rheumatoid arthritis difficult.

However, as Professor Hill pointed out to us yesterday, the main goal in the *treatment of the patient* with rheumatoid arthritis, which is very different from the *therapeutic evaluation of a drug*, is to enable him to carry on some or all of his usual activities. Several patients treated with this so-called placental implant have been so benefited, and have said "If I can stay this way the rest of my life, I'll be happy".

I believe the results in the small group described by Dr. Lintz seem to warrant further investigation, perhaps under somewhat better controlled conditions.

Postpartum Plasma in the Treatment of Rheumatoid Arthritis. By DAVID NEUSTADT, JACOB GEIGER, and OTTO STEINBROCKER, *New York, N.Y.*

This is a preliminary presentation of a pilot study to evaluate the clinical effects of postpartum plasma in active rheumatoid arthritis. The technique of Granirer was followed as closely as possible. Observations were made on a series of eleven patients. Seven patients completed an arbitrary course of 10 units of 250-300 ml. plasma administered intravenously at weekly intervals. Four patients are still undergoing treatment, but have had from five to nine transfusions. So far one patient has shown objective improvement, but he relapsed during therapy in spite of treatment being extended for an additional week (11 units).

No significant clinical or laboratory benefit has been noted. A control series, originally planned, was not conducted since the failure of the specific plasma made it unnecessary.

This study has failed to show any significant responsive trend or beneficial effect of postpartum plasma on the symptoms or course of active rheumatoid arthritis in our screening group.

Discussion.—DR. LOUIS W. GRANIRER (*Jamaica, N.Y.*): There must be some explanation for the ineffectiveness of these experiments. I note that the plasma was not pooled; in all our cases, we used pooled postpartum plasma.

I also failed to hear that the colour of the plasma was observed. Over a period of 4 years I have associated the characteristic greenish tint of postpartum plasma with the activity that most likely carries the antirheumatic substance. It would be logical to assume, therefore, that the antirheumatic substance was probably lost or destroyed during the preparation or storage of the plasma.

I should like to know when the blood was obtained, how the plasma was processed, whether it possessed the characteristic greenish tint, and how long it was stored?

We have observed that if a patient has had cortisone or ACTH therapy within a period of 8 or 10 weeks, the development of an effective convalescence is inhibited, but what the mechanism involved may be we do not know at present.

It might be interesting to point out, that when we use postpartum plasma 10 to 12 weeks after venesection, there is no evidence of any ACTH. The amount of ACTH present in fresh pooled postpartum plasma, according to our determinations, is 1·8 μg./ml. After 2 or 3 months, the ACTH has disappeared, and all we find are 50 μg./ml. corticosteroids. It is my feeling that the steroids have little or nothing to do with the patient's response.

Incidentally, the first patient we treated in 1948 has had a complete remission of 4 years with no treatment.

As to the percentage of our responses, I will say that 70 per cent. of our patients improved, and one-half of these showed a remission without treatment for anything from 3 months to 1 year.

The interesting part about postpartum plasma is that it is the most effective of all the things that we have used in psoriasis. Skin lesions and joints clear rapidly.

DR. JOHN LANSBURY (*Philadelphia, Pa.*): Unless the pregnancy effect is psychogenic, it seems that there must be a substance of intra-uterine origin which is capable of suppressing, though not curing, rheumatoid arthritis in most, but not all, pregnant women. The source of this substance is unknown, but it would seem to arise in the placenta and/or the foetus. Its mode of action is unknown. It may act *via* the maternal endocrines, in which case, if the substance could be isolated and used therapeutically, its use would presumably be complicated by unwanted manifestations of pregnancy which would be exceedingly inconvenient, especially in men.

If the mechanism of action is non-endocrinological, as it may well be, it is possible that this substance may eventually be isolated. So far all attempts to use pure pregnancy hormones have given negative results, although fleeting antirheumatic reaction has been reported by many authors. It would seem logical that the unknown antirheumatic factor may be most abundant in the placenta, but to find it will be exceedingly difficult.

If we look back on the history of the liver treatment for pernicious anaemia, we see that, first, crude liver was used by mouth, then liver extracts by mouth, then crude and later refined liver extracts by injection, and that it took nearly 25 years before the active principle B_{12} was isolated. All this in face of the fact that there was a clear end-point by which the therapeutic response could be detected, namely, the reticulocyte count. We have no such end-point in the case of rheumatoid arthritis, and the measurement of the minor degrees of improvement is exceedingly deceptive and misleading. But I believe that this field warrants further investigation, and because of its complexity it might best be studied by a co-operative programme.

DR. ABRAHAM S. GORDON (*Brooklyn, N.Y.*): I hoped that Dr. Spielberg would be here to discuss this paper. I feel responsible for the work that he has done, and, therefore, I have to take up his part in the discussion. We have, to date, twenty patients who have been followed with the placental blood serum method of therapy—not postpartum plasma. There must be some relationship between these two products. As Dr. Lansbury stated, something somewhere in the placenta is responsible for the improvement. We don't know what the active principle is, but we must continue investigations.

I have seen very remarkable results in more than half the patients studied. We have generally noticed that when patients are selected properly—and by properly, I mean of a certain age, and a certain reactive ability—the result will be much better. When older patients are treated, the results are poorer.

One patient who had been treated with cortisone for a long time without any benefit, had an excellent response with placental blood serum. One patient who had been treated by Dr. Granirer with his postpartum plasma without success had an excellent result with placental serum. I had a young girl, aged 25, with a history of severe rheumatoid arthritis of 6 years' duration, who had tried gold salts, cortisone, and everything else. She was a Class IV crippled patient, and yet she did very wel within 2 weeks after we started treatment with placental blood serum. She was able to move her joints briskly, although she had been so helpless that she could not even feed herself before. After 4 weeks we got her out of bed, but we did not have enough material for her and she had a relapse after 6 weeks, and is in hospital again now.

DR. NEUSTADT: In answer to Dr. Granirer, the venous blood was obtained 12 to 48 hours post partum. Pooling

was not done, as in the previous study, to obviate any reactions. Each patient was cross-matched as an added precaution. Two sterile cultures were obtained at 14-day intervals. The blood was stored at the most for 4 weeks, which is in accordance with Dr. Granirer's procedure.

The plasma mostly had a green opalescent colour.

In answer to Dr. Gordon, I have had no experience with placental blood serum, and cannot comment on that.

We have very great difficulty in obtaining the plasma, and from our experience so far, we have seen practically no benefit whatsoever.

Phenylbutazone—A Further Clinical Evaluation. By WILLIAM C. KUZELL, RALPH W. SCHAFFARZICK, W. EDWARD NAUGLER, GUY GAUDIN, and ELDON A. MANKLE, *San Francisco, Calif.*

A group of 800 patients with a variety of rheumatic diseases was treated orally and/or intramuscularly with phenylbutazone (Butazolidin) and/or a mixture of phenylbutazone and aminopyrin (Butapyrin or Irgapyrin). Some of these patients have been on continuous medication since November, 1950. A statistical evaluation of the therapeutic response and toxicity was made. The most striking clinical improvement was observed in acute and chronic gout. Among the other diseases which improved were ankylosing spondylitis, psoriasis with arthritis, painful shoulder, rheumatoid arthritis, and osteo-arthritis, in that order. Phenylbutazone was used in combination with gold and with cortisone in some instances with success. Toxic reactions were most frequent in the groups containing the largest number of older patients, but the toxic manifestations were much less among the gout patients generally. Toxic reactions included five instances of agranulocytosis with recovery. The most frequent toxic manifestations were gastro-intestinal and related to fluid retention. On cessation of medication in chronic rheumatic disorders, where a variable degree of improvement was observed, symptoms promptly returned in almost all instances.

Long-term Administration of Phenylbutazone in Rheumatoid Spondylitis. By ELMER E. YEOMAN, CHARLES A. L. STEPHENS, JR., DONALD F. HILL, WILLIAM L. GOODIN, and W. PAUL HOLBROOK, *Tucson, Ariz.*

We have previously reported that 80 per cent. of patients with rheumatoid spondylitis derived initial clinical improvement from phenylbutazone. In this report the early toxic reactions to the drug were emphasized.

Phenylbutazone has been administered continuously for 6 to 33 months to 38 patients, and to thirteen for 6 to 12 months, to ten for 12 to 18 months, to ten for 18 to 24 months, and to five for 24 to 33 months. Of these 37 patients are still taking phenylbutazone, with continued improvement both subjective and objective. In one patient the medication had to be discontinued because of the development of an acute bleeding duodenal ulcer.

Complications seen after 6 months' continuous medication were as follows: gastro-intestinal irritation (2); acute bleeding duodenal ulcer (1); thrombocytopenia of 50,000 platelets per cu.mm. (1); haematuria with renal calculi (3). In none except the second category was the medication permanently discontinued.

Ten of these patients had failed to maintain improvement on ACTH and/or cortisone. Phenylbutazone is the most effective agent we have used in the control of symptoms of rheumatoid spondylitis, but more experience must be gained before its permanent place in treating this disease can be determined.

Uncommon and Serious Reactions to Phenylbutazone—A Clinico-Pathologic Study. By EPHRAIM P. ENGLEMAN, MARCUS A. KRUPP, JAMES F. RINEHART, MAX FINE, EDWIN L. BRUCK, ALLEN B. BARBOUR, JOHN W. FARQUHAR, and ROBERT C. JONES, *San Francisco, Calif.*

The high incidence of the toxic effects of phenylbutazone is well established. In many instances these effects have been mild, but we have seen uncommon but serious reactions during the past year in seventeen patients, three of whom died.

Jaundice occurred in five (one died); pathological examination at *post mortem* and by liver biopsy revealed toxic hepatitis in two patients and toxic cirrhosis in one. Heart failure was observed in four patients; two showed significant salt-and-water retention superimposed on pre-existing heart disease; heart failure was clinically unexplained in the remaining two patients, one of whom died. *Post-mortem* studies disclosed a profound, interstitial myocarditis and unusual alterations were also present in the liver and kidneys.

Additional serious reactions during therapy with phenylbutazone included optic neuritis with residual blindness or defective visual fields (2); transient, toxic psychosis (2); gastro-intestinal ulceration, previously unsuspected (3); thrombocytopenic purpura (4); agranulocytosis (2) one of whom died.

In all seventeen patients, phenylbutazone was given for 2 days to 4 weeks in a daily oral dose of 0·3-0·8 g. Routine clinical precautions were exercised and in each patient, except one, the drug was stopped at the earliest manifestation of toxicity. It is obvious that serious, even fatal, reactions to phenylbutazone are unpredictable despite cautious administration. If the occurrence of the serious reactions reported herein is confirmed by others, it will be necessary to reconsider the place of phenylbutazone in therapy.

Discussion.—DR. OTTO STEINBROCKER (*New York, N.Y.*): We have had wide swings from the first paper to the last paper on the subject of phenylbutazone. My associates and I have so far administered the drug to 500-600 patients for short or long terms, and our results in a variety of conditions have continued to be quite favourable.

We have been fortunate so far in not having any serious toxic reactions other than one presumptive gastric haemorrhage with good recovery and one case of hepatitis which we could not be sure was due to the drug. We have encountered nearly all the minor reactions mentioned by the speakers in 30 per cent. of our patients. From the untoward effects encountered, particularly the serious ones, it would appear to be a matter of individual deficiency, idiosyncrasy, or hypersensitivity rather than of any predictable characteristic of the drug. A report of new fo ms of toxicity, like Dr. Engleman's,

suggests that the full range of reactions of Butazolidin remains to be determined.

There is general agreement in nearly all reports that phenylbutazone is an effective agent in our field of interest, as the first two papers stated, but to-day the crux of the matter is the question of toxicity. Are the hazards of this substance such as to cancel the benefits?

To date, in the U.S.A., the most serious and disturbing reactions, to my knowledge, have been twelve cases of agranulocytosis with three fatalities; four instances of hepatitis with one fatality; the optic neuritis discussed already, and a number of lesser but potentially serious cardiovascular, haematological, and gastro-intestinal complications. Not all toxic reactions and fatalities are reported and there may be more to come. It is true, too, that a number of untoward reactions, of which it probably is not guilty, have been attributed to Butazolidin.

Now, after these grim facts, the subject must be balanced with further information to arrive at a true evaluation. According to the manufacturers, who, at my request through Dr. Hemming, attempted to estimate the total amount of Butazolidin distributed and recorded through commercial channels, it is their conservative calculation, on the arbitrary basis of an average dosage of 600 mg. for 30 days, that the preparation has been administered to 750,000 patients. To lean back in our own interpretation of this information, without disparagement of these data, we might assume that at least 350,000 individuals have been the source of the mishaps discussed. Of course, it is difficult to console a toxic patient or his family with statistics, but a fair assessment at this point for good as well as for evil cannot be made in any other way.

It is plain that Butazolidin is not aspirin. Experience so far shows that it is a promising addition to our resources, but it should not be prescribed for trivialities and should be reserved for major musculoskeletal disease, with a respect for the contra-indications already apparent and with due precautions against the toxic potentialities which are probably not yet completely delineated.

DR. I. N. DUBIN (*Washington, D.C.*): Dr. Engleman was kind enough to send tissues of three patients to the Armed Forces Institute of Pathology, so that we could compare his material with that of the Registry of Hepatic Pathology, where we have 4,000 needle biopsy specimens of the liver. His three cases fell into two groups:

(1) arteritis and diffuse granulomatous myocarditis;
(2) jaundice.

The first I will say little about except that the lesions seen in the arteries and heart are indistinguishable from the allergic type of response seen in drug hypersensitivity following treatment with sulphonamides and other drugs. This patient had only a mild hepatic lesion, characterized by a slight degree of centrolobular necrosis and fatty metamorphosis.

The other two patients had a peculiar form of hepatitis. One recovered and in this case we have only a needle biopsy specimen of liver. The other died of myocardial infarction and in this case we have both liver biopsy and autopsy material. In both cases, the hepatic lesion was characterized by focal necrosis of liver with some tendency towards exaggeration of necrosis in centrolobular zones; also present were bile stasis and portal inflammation in which neutrophil leucocytes were fairly prominent. The histopathological pattern was definitely not that of viral hepatitis. Moreover, it was not the picture produced by known hepatotoxins such as halogenated hydrocarbons, phosphorus, arsenic, and the like.

It was difficult to decide what was the cause of the hepatitis. From a clinical point of view it appears that phenylbutazone was the causative agent, but the pathologist would prefer to reserve judgement until more experience has accumulated. Judging from the statistics bandied about this afternoon, the clinicians are using the drug so widely that we can expect such information to be available soon.

DR. CHARLEY J. SMYTH (*Denver, Colo.*): During the past 2 years we have given this drug to approximately 75 patients with rheumatoid arthritis and six patients with acute gout. At first, we used daily doses of 600 to 1,200 mg., but recently we were able to obtain comparable symptomatic response with 300 to 400 mg. per day. The results in rheumatoid arthritis in our experience are largely symptomatic. In a rare instance, in an occasional case, we do see definite objective improvement, but it is impossible to say whether this is due to the drug or to the natural course of the illness. Fortunately, we have had no serious toxic effects so far.

In the six patients with gouty arthritis, there was a prompt clearing of both symptoms and signs of disease, and this response was comparable to that which has usually followed colchicine therapy.

Of special interest was the influence of Butazolidin upon urate metabolism. In gouty patients receiving doses of 800 to 1,200 mg., there was a consistent diuresis of uric acid, and this was shown to occur about the third to the fifth day of therapy. Comparable studies are now under way with benemid and salicylates.

The selective influence of this drug is remarkable. The available evidence indicates that gout and perhaps rheumatoid spondylitis do respond somewhat differently from some of the other muscular-skeletal diseases. I think this Society should weigh the evidence very carefully; it is a serious obligation to our colleagues who look to us for advice that we study this drug to determine whether the clinical risk is worth the benefit derived.

DR. WILLIAM B. RAWLS (*New York, N.Y.*): We have never given more than 600 mg. in any one case, our usual dose being 100 mg. three times a day. We do a weekly blood count for the first 3 weeks and then every 2 weeks.

The toxic manifestations we have seen include neuropsychiatric changes (we have had patients with depression), nervousness, insomnia, numbness and tingling of the hands and fingers, weakness in the legs, instability of gait, and dizziness. We have noted that patients with numbness and tingling and instability of gait have recovered more quickly when we have given 1,000 mg. B_{12} for 4 or 5 days.

We noted personality changes with threats of suicide, ulcers in the mouth, and sore tongue.

We have encountered blurred vision, but without serious or permanent results. There were also uncontrollable, unexplainable headaches, which were relieved when phenylbutazone was stopped and recurred when it was reinstituted.

There was oedema of the feet and legs, with both long-term and short-term treatment, coronary thrombosis, dyspnoea, and water retention. One patient who had been operated on for cancer of the breast had no oedema of the arm prior to taking phenylbutazone, and we were not able to bring about a return to normal.

Several patients had dermatitis, urticaria, and angioneurotic oedema; one had activation of a peptic ulcer

with haemorrhage, three haematuria, and frequency of micturition. In the older women incontinence occurred which was controlled after omitting the drug, and there were also several patients who experienced reactivation of an old prostatitis.

I do not know whether the headaches represent a mild encephalitis. We used antihistamines in patients with dermatitis and then phenylbutazone with good results.

Two characteristics of the drug may help to avoid undesired effects: (1) any benefit is usually noticed within 2 or 3 days; (2) toxicity mostly occurs after longer use than 2 or 3 days. If phenylbutazone is not used unless it has a distinctly superior analgesic effect, many difficulties can be avoided.

DR. CHARLES L. STEINBERG (*Rochester, N.Y.*): Dr. Engleman asked me to say a few words on a paper by Drs M. G. Bohrod, A. I. Roodenburg, and myself.*

A 52-year-old white female received 400 mg. Butazolidin daily for 26 days, and one week after cessation of the drug, developed agranulocytosis and died. The granulocytes had a peculiar clumping arrangement which has been described as occurring in pyramidon poisoning. At autopsy the appearance of the marrow gave the impression that, if it had been possible to keep the patient alive a little longer, she would have survived, because the bone marrow was loaded with granulocytes. Another interesting finding was the adrenal cortex, where the cells were arranged as if we had aciniform. Sections of the myocardium showed many granulomata with swelling and fibrinoid degeneration of the collagen network.

DR. HOLBROOK: Dr. Engleman has reported every toxicity that he has observed in which Butazolidin was suspected as the toxic agent, and I do not know why his figures differ so widely from ours. It may be due to the small doses we used, to a different selection of cases, or perhaps to good fortune. We have observed more than three hundred patients with various rheumatic diseases on Butazolidin, and have not seen one case of optic atrophy, jaundice, or agranulocytosis.

We have expressed our concern about the toxicity of this drug. The previous reports of toxic amblyopia stimulated a careful study of our longest-term patients: 31 who had been on the drug for more than a year were carefully examined by Dr. Michael J. O'Connor of Tucson, who is an ophthalmologist, without finding any evidence of optic atrophy. One man with a small scotoma, who had a history of previous double vision, is a suspected case of multiple sclerosis.

In summary, we feel that this drug is extremely worthwhile in gout and in rheumatoid spondylitis, and that with proper selection of patients and alertness to possible toxic effects, the benefit far exceeds the risk.

DR. JOHN W. GRAY (*Newark, N.J.*): Last week at the New Jersey State Meeting we reported our evaluation of phenylbutazone therapy in various conditions. Its prophylactic effect in seventeen gouty arthritic cases was particularly impressive. Its use in controlling acute attacks is recognized, but its use in the prevention of attacks has not been sufficiently emphasized. The usual gout treatment had failed to prevent repeated recurrences in our seventeen cases, but since we started using phenylbutazone, more than a year ago, only one case has had one attack, and he "forgot to take the red pill". All the rest were maintained without attacks or toxic effects on 100 mg. daily. We are now trying 50-mg. doses.

DR. KUZELL: Optic atrophy is so serious that I should like Dr. Engleman to give more detailed information on these patients, particularly the evaluation by Professor Maumenee, Professor of Ophthalmology at Stanford University.

DR. ENGLEMAN: Dr. Maumenee was recently asked by the Geigy Corporation to see the two patients who developed optic neuritis during the administration of phenylbutazone. He confirmed the diagnosis of optic atrophy in one patient and optic pallor in the other. The first patient showed prominent cupping of the disks, suggesting possible concomitant glaucoma, although intra-ocular pressure readings were not performed. It must be emphasized that there was no evidence of glaucoma at the onset of the eye disease one year previously. There is no question that loss of vision in the first patient and abnormal visual fields in the second are the direct results of optic neuritis.

We have heard of only one other patient in whom optic neuritis was observed during the administration of phenylbutazone, and at present time, we can only suspect phenylbutazone as the cause. But there can be little doubt that complications involving bone marrow, gastrointestinal tract, liver, and heart are actually toxic reactions to this drug. They have occurred unpredictably and without warning, despite the precautions mentioned by the discussants. In view of these possible side-effects, it is for each of us to answer the question whether the therapeutic effects justify the risk?

* (1953). *J. Amer. med. Ass.*, **152**, 33.

BOOK REVIEWS

Physical Medicine and Rehabilitation. Edited by Basil Kiernander. 1953. Pp. 610, 26 figs, 11 tables. Blackwell, Oxford. (63*s*.)

The editor makes the point in his foreword that this book is written for clinicians in general, and not for specialists of physical medicine. The wide range of subjects indicates the enormous field in which physical methods of diagnosis and treatment are employed, and 50 per cent. of the contributors are not physical medicine specialists.

The claim that the basic sciences are studied in some detail is, unfortunately, not borne out by the text. In introducing physical methods to clinicians in other specialties it might be expected that full attention would be given to the rationale of physical treatment, and the physiological effects of potent physiotherapeutic measures in health and disease. However, the author of the chapter on applied physiology has the unenviable and impossible task of compressing his contribution into 15 pages. Some physics is included in Chapter XII, which is devoted principally to describing techniques, ten of its sixty pages being given up to the applications of the direct current and iontophoresis, which to say the least, shows marked lack of balance.

All the chapters on the various aspects of rehabilitation are good—that on geriatric rehabilitation particularly comprehensive and thoughtful. The section by Howard Rusk on the rehabilitation of the hemiplegic is a model and in a very few pages brings in a wealth of useful detail. Professor Bowden's chapter on the neuromuscular disorders is characteristically accurate, well documented, and original.

The rheumatic diseases in general are well covered, and the list of exercises appended for continuation treatment in the home might well be generally copied. The emphasis on home treatment and home-made apparatus is one which will not be welcomed by many in Great Britain, although it represents current American practice.

A major criticism of the book is the limited space allowed to each author, and the fact that where expansion is permitted, it is not always used to the best advantage. Treatments of doubtful value are included in detail, whilst some generally accepted are not considered. For example, in non-articular rheumatism the only treatment described is heat and heavy massage.

Although hydrotherapy in the management of the rheumatic diseases and poliomyelitis is discussed, no mention is made of walking re-education in the deep pool as a preliminary to weight bearing.

Subjects which usefully could be expanded are cerebral palsy, rehabilitation in heart disease, and antenatal and postnatal exercises, all important aspects of physical medicine which here receive rather brusque treatment.

The team of contributors is drawn from England, Canada, and the U.S.A., and there is a valuable introduction by Lord Horder. The book is well printed and attractively produced, and the illustrations and diagrams, though few in number, are well chosen. However, errors in spelling are too frequent (e.g. evapourating, p. 397; collatral, p. 549; mannually, p. 557; and three variations of one author's name—Frenkel, p. 275, Fruenkel, p. 606, Fränkel, index), and the listed references, so important in a condensed book of this type are disappointing.

The book is one which can be recommended to all generally interested in physical methods, and contains much of interest and value to students and specialists in physical medicine.

R. HARRIS.

Synovial Fluid Changes in Joint Disease. By M. W. Ropes and W. Bauer. 1953. Pp. 150, 13 figs, 15 tables, bibl. Harvard University Press; Geoffrey Cumberlege, London. (25*s*.)

This exhaustive monograph, embodying the authors' unrivalled experience of joint fluids in health and disease, is a mine of information. Present knowledge of the constitution and physiology of normal joint fluid is first described and thereafter the possible alterations in disease. Abnormal fluids are classified into three groups: those of traumatic origin, those of rheumatoid arthritis or of infectious origin, and those with mixed features. Each group is discussed with a wealth of detail. The book concludes with a short chapter on the diagnostic value of joint aspiration, an extensive bibliography, and a large, separate Table summarizing the authors' findings.

This book brings together a great deal of information in a small compass, and, though highly condensed, is clearly written. It will be a particularly valuable addition to the pathologist's library, for reference and guidance in the selection of appropriate investigations and the interpretation of their results, but all who deal with joint disease would do well to have this book at hand.

M. R. JEFFREY.

Traité de Médicine, Vol. XVII Maladies des Muscles, des Os, des Articulations, et Rhumatismes. By P. Chiche, F. Coste, A. Escalier, J. La Presle, F. Layani, M. Lelong, J. A. Lièvre, R. Leriche, R. Mallet, P. Padovani, et H. Thiers. With addenda to Vol. I (V. de Lavergne and P. Sédallian), Vol. II (V. de Lavergne), Vol. IV (P. Bertoye and M. Bernheim), Vol. V (P. Blamoutier, P. Sédallian, and C. Roubier), Vol. XII (E. Benhamon and A. Aschkénasy), and Vol. XVII (H. Thiers), and alphabetical index to the seventeen volumes. 1953. Pp. 1,062, 237 figs. Masson, Paris. (*Frs* 6,100; £6 10*s*.)

The seventeenth and last volume of this *System of Medicine* is devoted to diseases of muscle, bone, joints and chronic rheumatism. It also contains addenda to

some of the previous volumes and an index of 240 pages replete with eponymous diseases and illustrious names (that of Heberden being, however, unfortunately omitted). The publishers claim that this volume completes "l'ouvrage le plus important et le plus riche de substance qui ait été publié au cours des trois dernières années"; it is also claimed that each volume is so arranged that it can be bought and used separately as a monograph, but the presence of the index and important addenda in the last volume tends to emphasize the unity of the series. As a work of reference, for which it is primarily intended, this compilation suffers from a number of faults which, no doubt, will be rectified in later editions. Fanconi's syndrome, for instance, is not described in this volume, but the index tells us that it is to be found in Vol. XII (devoted to blood diseases); similarly, osteomyelitis is placed in Vol. I (infectious diseases), and scleroderma in Vol. XIII (diseases of endocrine glands). Neither disseminated lupus erythematosus nor osteoid osteoma is described in Vol. XVII, and neither can be traced in the index. Four pages are devoted to cortisone and ACTH; these, though adequate for a text-book, will hardly satisfy a French rheumatologist, when, in the same library, he can pick up a 414-page volume by Coste, Cayla, and Delbarre on "Cortisone et Corticostimuline (ACTH) en Rhumatologie", or Copeman's "Cortisone and ACTH in Clinical Practice". At the same time one can sympathize with the editors in their attempt to keep the work within reasonable bounds.

The print is good and the quality of the paper, though not uniform, is satisfactory. Each disease is introduced by a short and informative historical survey which stimulates interest. Bibliographical references are usually indicated by a number in the text and a footnote, but too frequently the reader is left to make what he can of a string of names only. Thus, when describing sacralization of L5, one reads that "c'est depuis 1910, en effet, que Adams, Goldwait, Kleinschmidt ont étudié les conséquences clinique de la malformation. À leur suite, et après les observations de Denucé, Calve, Japiot . . ." (p. 208).

This work will, of course, have a limited appeal, but the magnitude of the task undertaken is so great that the editors and publishers can take justifiable pride in their achievement.

DAVID PREISKEL.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

REPORT OF THE SECRETARY GENERAL, AUGUST 23, 1953

This is the last time I make a report in my capacity of Secretary General.

Both the Secretary, Dr. Kalbak, and myself have decided to resign our offices as from the termination of this Congress. We have both of us served in the Secretariat General of Ligue Européenne since its establishment in 1946; that is, for seven years; and we find it reasonable that new hands and new initiative should take over. I would therefore take the liberty of making a somewhat more elaborate report on the development of rheumatology since December, 1946, when Professor Jarløv, Director Bornemann, Dr. Kalbak, and myself made a tour through most of the countries of Western Europe, obtaining, through conferences with the various national rheumatological societies, agreements that made possible the establishment of Ligue Européenne concurrently with the reorganization of Ligue Internationale. I propose to deal in somewhat greater detail with the period following the last congress in Barcelona in 1951.

The aim of our organization is to further in every way the fight against the rheumatic diseases. Above all, we should support and promote scientific research. We do so by arranging congresses, by contributing to scientific periodicals, and by assisting personal contact and co-operation between research workers of different countries. We must also strive for better and more up-to-date tuition in rheumatology at the universities and medical schools, and stimulate whatever efforts are being made to provide better hospital facilities for the treatment of the rheumatic diseases.

(1) As far as *scientific research* is concerned, the period has been characterized by both initiative and progress. What especially captured our interest during the first years was the relation between the haemolytic streptococcal infection and certain rheumatic diseases, and much light was thrown upon this problem.

Then, in 1949, followed Hench and Kendall's epoch-marking observation of the influence of the suprarenal-cortex hormones. This opened up an entirely novel view of the pathology of the rheumatic diseases. It was estab-

lished that the mesenchyma functions as an independent organic system; and that, in the rheumatic diseases, it is this system that is particularly affected. It was found that the collagenous connective tissue in particular was attacked, and by degrees the designation of collagenoses has been adopted into the language.

During the years 1949-51, in all the laboratories and hospitals of the world countless therapeutical experiments were made with varying degrees of success. In the last 2 years, these researches have been directed into a more profitable channel. Detail by detail, the problems are being cleared up, in regard to both the cellular processes and the morphology, physiology, and biochemistry of the larger tissue systems. Immunological research has also been influenced by these novel views. We begin to think that *the basic research within our specialty is now approaching the core of the problem.*

It cannot be sufficiently emphasized how vitally important to the future of rheumatology as a clinical discipline is a continued and keen interest in the basic research. Equally important is the maintenance of close co-operation between the rheumatological hospital wards, ambulatoria, and sanatoria, and the biochemical, physiological, climatological, pathological, and immunobiological laboratories. New observations in theoretical research can be tried out rapidly in the practical treatment of patients, while on the other hand clinical therapy can still be made the subject of critical research.

However fine, co-operation within one hospital or research team is not everything; co-operation should be practised between all research groups and hospital wards in the world. Science is universal and international; new observations are the property of everybody; and the best result is achieved only if all the world co-operates to reach a common objective. Here lies the justification and chief task of our organization: the creation of personal contact between all rheumatological research workers of the world. This may be achieved through congresses, conferences, and study tours, and, most important of all, through publication in our scientific periodicals of the results of our researches.

The *Annals of the Rheumatic Diseases* is our central organ serving this purpose. I call upon each and every one of our members to contribute to the best of his ability towards making the "Annals" the central rheumatological scientific periodical of the world. This periodical has, in the past three years, grown to a high scientific standard, and its contents now cover all branches of rheumatological research. I in no way under-estimate our other rheumatological periodicals, of which especially the *Revue du Rhumatisme*, *Zeitschrift für Rheumaforschung*, *Revista Española de Rheumatismo*, and *Acta Physiotherapica et Rheumatologica Belgica*, are outstanding, but I want to emphasize the necessity of having a common central rheumatological periodical which should serve as the official organ of our international organization.

One of the most burning problems of the day is that of *nomenclature*. The international committee engaged on this task will presumably soon be in a position to make its report. In my capacity of Secretary General, and from this rostrum, I wish to urge everybody to show tolerance and magnanimity when the said report appears. We cannot create an international nomenclature unless each country is prepared to yield on certain points. No country has a right to demand that *her* special view should dominate in the international terminology. Personally, I hope that we may agree on a common nomenclature based on *Latin*, with freedom for individual countries to employ such local translations as may be found practical.

(2) *Tuition in rheumatology in medical colleges and university departments* has been appreciably extended, in particular by *the establishment of professorships or other tutorial posts in rheumatology*.

The oldest special rheumatology ward in a university hospital seems to be that at the Mayo Clinic at Rochester, U.S.A., established in 1926 under P. S. Hench. The oldest one in Europe seems to be that of the University of Lund, Sweden, where, in 1936, I was appointed lecturer (docent) in rheumatology and put in charge of the ward under the professor of internal medicine. Only in 1947 did the rheumatological ward become independent, and at the same time I was appointed ordinary university teacher as professor associate in rheumatology. In 1936 L. von Pap was appointed docent in rheumatology at the University of Budapest and worked there some years. In 1945 E. Jonsson was appointed docent in rheumatology at Carolin Institute of Stockholm.

In 1949, F. Coste was appointed professor in clinical rheumatology at the University of Paris. For several years previous to this, however, he had been prof. agrégé at that university, as well as chief of a rheumatological special ward at the Hôpital Cochin. S. de Sèze is prof. agrégé at the same university, and head of a similar ward at the Hôpital Lariboisière.

In 1951, L. Michotte was appointed prof. agrégé in rheumatology at the University of Louvain, and A. Masturzo was similarly appointed at the University of Naples.*

Concurrently with these, more official appointments, special tuition in rheumatology has been introduced at many universities. In *Great Britain* the first rheumatism department at a General Hospital was established as early as 1938 at the West London Hospital (with Dr. W. S. C. Copeman as chief), and rheumatology now is a compulsory subject for the final examination at the London Hospital (Dr. W. S. Tegner); non-compulsory tuition is provided at the universities of Edinburgh, Manchester, Leeds, and Bristol. In *Belgium*, such tuition is provided at Brussels, Liége, Ghent, and Antwerp; in the *Netherlands*, at Amsterdam, Leyden, Utrecht, Nijmegen, and Gröningen; in *Switzerland*, at Geneva and Zurich; in *Italy*, at Milan and Genoa; in *Spain*, at Barcelona and Madrid; in *Portugal*, at Lisbon; in *Finland*, at Helsingfors; and, in *Norway*, at Oslo.

Our objective should be *a professorship or other regular tuition in rheumatology at every university medical school*, and the subject should be compulsory for the final examination with a syllabus as comprehensive as in Paris or London. Only then will the general practitioner

* Since this report was presented a further Chair of Rheumatology has been established at the University of Manchester, England. See p. 358 of this issue. (Ed.)

receive sufficient knowledge of, and develop sufficient interest in, the rheumatic diseases, and only then will the fight against these diseases become effective.

At the 25th anniversary of the Ligue Française in March, 1953, Dr. Galmiche and Dr. Robin delivered lectures on the importance of *rheumatology as a medical specialty*. They emphasized that without such specialists we would make little progress, and they stressed the necessity of having doctors who specialize in such diseases only and make the fight against them the aim of their lives. I quite concur in this opinion. *Rheumatology*, in every country, *should be recognized as an independent specialty*, and the training course should include not only a sufficiency of internal medicine, orthopaedics, and physical medicine, but also a term of practice in a regular rheumatological special ward.

(3) *Rheumatological hospital wards* have been established here and there in various countries since 1946. In some the emphasis is laid on internal medicine, and in others on orthopaedics, and others give chief place to physiotherapy. It is very important that all these tendencies should be co-ordinated to follow a common course, which, though comprising all three basic disciplines, has internal medicine as its chief and dominating characteristic.

It would lead too far if I were to discuss here the many practical therapeutical advances and problems that have assumed topical interest, but I will mention just a few.

The therapeutic value of ACTH, cortisone, and the other steroids has become stabilized at a sensible level. At first, rather too high expectations were formed. We know to-day that cortisone especially is an important therapeutic aid, but that it cannot be employed uncritically, and that the problem of proper dosing requires considerable special experience. This, too, emphasizes the necessity of having rheumatological specialists.

Also, the value of *supervising articular function* in the active phase of the disease and of combating contracture by means of reasonable *physiotherapy* and subsequent *rehabilitation* has become increasingly clear.

The Ligue Européenne at present comprises nineteen national leagues, as yet, unfortunately, contact with our fellow workers in Eastern Europe is exceedingly limited. Two of our member leagues: the Ligue Belge and the Ligue Française, have recently celebrated their twenty-fifth anniversaries, and we desire to extend to these two societies our cordial congratulations, thanking them for their excellent and important work, and for their contributions to rheumatological research and to the development of the specialty.

Wishing that the Ligue Européenne, and hence also the campaign against the rheumatic diseases, may enjoy continued progress, good fortune, and success, I now conclude my report, leaving the Secretariat General to my successor. GUNNAR EDSTRÖM.

Résumé

Depuis 1946, la Ligue Européenne contre le Rhumatisme existe comme organisation indépendante sous la Ligue Internationale. Pendant ce temps, la Ligue Européenne a fait un grand progrès, tant au point de vue d'organisation qu'au point de vue de science. Aujourd'hui, la Ligue Européenne comprend dix-neuf ligues nationales en Europe.

Parmi le grand nombre de poussées scientifiques de haute importance, au cours de cet espace de temps, le nouveau gain le plus important est, sans doute, la constatation certaine que le tissu mésenchymanteux—"le tissu conjonctif"—constitue le point d'attaque primaire des maladies rhumatismales. A l'avenir, il nous faudra donc mettre tout en oeuvre pour une large investigation de base de cet organe tissulaire, et la tâche principale de la Ligue Européenne sera donc de favoriser et d'inspirer cette investigation de base.

Nous devrons poursuivre notre travail par un contact mutuel aussi étroit que possible, d'une part par des réunions régionales moins importantes, d'autre part par des congrès européens. Le trait d'union quotidien devra être la revue périodicale, *Annals of the Rheumatic Diseases*, qui représent, en réalité, notre figure officielle vers le dehors et à la quelle suppléent, d'une manière excellente, nos revues à empreinte plutôt locale. La Ligue Européenne devra aussi contribuer à résoudre le problème de la nomenclature, comme un essai de nouer ultérieurement les rhumatologistes du monde entier.

Un élément constitutif est l'enseignement de la rhumatologie. Sur ce point, la Ligue Européenne devra favoriser tout effort tendant à l'introduction d'un tel enseignement spécialisé dans toutes les universités et les écoles supérieures de médecine de l'Europe. Ce n'est pas le corps enseignant qui fait défaut, et à la longue, on devra créer des chaires régulières de rhumatologie. De la même façon, la Ligue Européenne devra, de toutes ses forces, favoriser la création de services spéciaux rhumatologiques.

Le plus grand progrès de thérapeutique pratique de la période écoulée a été l'observation par Hench et Kendall sur l'influence favorable des hormones corticosurrénales sur les maladies rhumatismales. Cette observation clinique est aujourd'hui clarifiée jusqu'à ce point, et nous savons qu'il est dangereux d'employer ces hormones sans critique. Cette observation, cependant, a ouvert des voies toutes nouvelles et constitue un jalon tant dans la lutte contre les maladies rhumatismales que dans l'investigation de théorie expérimentale.

Auszug

Die "Ligue Européenne" besteht jetzt seit dem Jahre 1946 als selbststandige Organisationunter der Ligue Internationale. Während dieser Zeit hat die Ligue Européenne sowohl organisatorisch als wissenschaftlich grosse Fortschritte gemacht. Die Ligue Européenne besteht jetzt aus neunzehn europäischen National-Vereinen.

Unter den vielen wissenschaftlichen Vorstössen während dieser Zeit ist die grösste neue Errungenschaft zweifelsohne die sichere Feststellung der Tatsache, dass das mesenchymale Gewebe—das "Bindegewebe"—die primäre Angriffstelle der rheumatischen Krankheiten ist. Deshalb müssen wir in der Zukunft, alles auf eine breite basale Erforschung dieses Gewebeorganes einsetzen, und

die Hauptaufgabe der Ligue Européenne wird darin bestehen, diese Basalforschung zu unterstützen und anzuregen.

Wir müssen unsere Arbeit in möglichst gegenseitiger enger Zusammenarbeit fortsetzen, teils durch kleinere regionale Sitzungen, teils durch europäische Kongresse. Die *Annals of the Rheumatic Diseases*, die in der Tat unser offizielles Gesicht nach aussen hin sind, und die unsere mehr lokalgeprägten Zeitschriften auf vorzügliche Art und Weise ergänzen, müssen das tägliche Bindeglied sein. Auch bei der Lösung des Nomenklaturproblems muss die Ligue Européenne mithelfen, in dem diese Lösung ja gern die Rheumatologen der ganzen Welt enger zusammenknüpfen sollte.

Ein Hauptfaktor ist der Unterricht in Rheumatologie. Es muss deshalb die Aufgabe der Ligue Européenne sein, jede Bestrebung zur Einführung eines solchen Sonderunterrichts bei allen europäischen Universitäten und medizinischen Hochschulen zu unterstützen. An Lehrerkräften fehlt es nicht, und im Laufe der Zeit müssen ordentliche Professorate in Rheumatologie errichtet werden. In derselben Weise muss die Ligue Européenne mit aller Kraft die Errichtung rheumatologischer spezialabteilungen unterstützen.

Der grösste praktisch-therapeutische Fortschrifft während der verflossenen Zeit stellt die Beaobachtung Hench and Kendall von der günstigen Wirkung der Nebennierenhormone den rheumatischen Krankheiten gegenüber dar. Die klinische Beobachtung ist jetzt so weit abgeklärt, dass wir wissen, dass es gefährlich ist, diese Hormone unkritisch zu benutzen. Diese Beobachung hat indessen ganz neue Wege erschlossen und bildet ein Markstein sowohl in der Bekämpfung der rheumatischen Krankheiten als in der experimentell-theoretischen Forschung.

Sumario

La "Ligue Européenne" existe ya desde 1946 como organización independiente formando parte de la Ligue Internationale. En este período ha progresado mucho la Ligue Européenne con respecto a su organización ya a su contribución cientifica.

Entre los muchos e importantes resultados el más feliz conseguido en este período es sin duda la comprobación indiscutible de que el tejido mesenquimical—el "tejido conjuntivo" es el punto de ataque primario de las enfermedades reumática. Por lo tanto debemos en el porvenir concentrar nuestros esfuerzos en una amplia investigación básica de este órgano, y nuestra obra principal será la de apoyar e inspirar esta investigación fundamental.

Debemos continuar nuestro trabajo en el contacto mutuo más estrecho posible, parte mediante reuniones regionales de menor importancia y parte mediante congresos europeos. El lazo cotidiano debe ser los *Annals of the Rheumatic Diseases*, que en realidad es nuestra cara official hacia afuera, suplidos de modo excelente por nuestras revistas de carácter más regional. La Ligue Européenne se presta también como colaboradora en el problema de nomenclatura en vista de contribuir a la reunión de los reumatólogos de todo el mundo.

Un factor principal es la enseñanza en la reumatologia. En esto debe apoyar la Ligue Européenne cualquier esfuerzo por introducir tal enseñanza en las universidades y escuelas altas europeas. Maestros no nos faltan y andando el tiempo habrá que fundar cátedras de reumatologia. Del mismo modo tendra la Ligue Européenne que secundar con toda energia la creación de equipos reumatológicos especiales.

El mayor progreso práctico-terapéutico conseguido en el período transcurrido ha sido la observación por Hench e Kendall del efecto favorable fe los hormones de la capa cortical de las cápsulas suprarenales ante las enfermedades reumáticas. Esta observación clínica se ha aclarado tanto que ya sabemos que es peligroso aplicar sin crítica tales hormones. Sin embargo ha abierto dicha observación nuevos caminos no sospechados y queda un jalón lo mismo en la lucha contrá las enfermedades reumáticas como en la investigación experimenta-teórica.

FIRST BRITISH CHAIR IN RHEUMATOLOGY

The Council of the University of Manchester have announced that they have agreed to establish a Chair in Rheumatology, with the help of an annual grant of £3,000 from the Empire Rheumatism Council, as from December 25, 1953.

Dr. J. H. Kellgren, F.R.C.P., has been elected as the first Professor.

This is the first Chair in this specialty to be established within the British Commonwealth.

HEBERDEN SOCIETY

Clinical Meetings.—A meeting was held in the Dept of Physical Medicine, University College Hospital, London, on October 23, 1953. The greatest praise is due to Professor M. L. Rosenheim, Dr. Hugh Burt, and members of their departments for their meticulous care in organizing the meeting.

Four cases illustrating pitfalls in the diagnosis of backache (spinal tuberculosis, secondary carcinomatosis of the sacro-iliac joint from a primary pancreatic tumour, and carcinoma of the pancreas, and a penetrating duodenal ulcer both involving retroperitoneal structures) were shown by Drs Burt and S. Mattingley.

Drs C. E. Dent and B. Senior showed five cases of metabolic bone disease presenting as vaguely localized pain: steatorrhoea with osteomalacia, vitamin D deficiency with osteomalacia, idiopathic osteoporosis, Fanconi syndrome, and hypothyroidism causing epiphyseal dysgenesis and dwarfism.

Four most unusual and interesting cases of the hypercalcaemic syndrome in sarcoidosis were shown by Prof. Rosenheim and Dr. J. Anderson; it is of interest to note that the lung lesions and function had improved on cortisone therapy and were being maintained on a low dosage.

A most instructive collection of aids and appliances for the arthritic patient was demonstrated by Drs W. D. Fletcher and D. A. Kininmonth, some of the items having been made in the occupational therapy department and loaned for the meeting.

A popular innovation was a diagnostic quiz. Twelve complex and difficult *x* rays (including examples of conditions, such as yaws and collapsed vertebrae caused by tetanus, brought back by Prof. M. L. Rosenheim from the Far East) were shown for diagnosis.

In conclusion Professor Tunbridge thanked the organizers on behalf of the Heberden Society for one of the best clinical meetings that members had ever had.

At a meeting held at the Royal College of Surgeons, London, on December 5, 1953, papers were given on the following subjects:

Dr. A. Freedman (introduced by Dr. F. S. Bach, *London*): Mepacrin and Butazolidin in Rheumatoid Arthritis.

Dr. H. F. West (*Sheffield*): Purified ACTH Gel—Clinical and Chemical Assays in Rheumatoid Patients.

Dr. J. Sharp (*Manchester*): Familial Vascular, Ligamentous, and Articular Calcification.

Dr. M. Thompson (introduced by Dr. J. J. R. Duthie, *Edinburgh*): Osteitis Condensans Ilii and Ankylosing Spondylitis.

Dr. P. W. Darby (introduced by Prof. N. F. Maclagan, *London*): Liver Function Tests in Rheumatoid Arthritis.

Heberden Oration.—This was given on December 4, 1953, by Sir Russell Brain, who took as his subject, "Spondylosis: The Known and the Unknown".

SOCIETÀ ITALIANA DI RHEUMATOLOGIA

SECOND ROME RHEUMATOLOGY DAY, 1954

Three scientific sessions will be held in Rome on February 13 and 14, 1954. Lectures will be given by Prof. E. Martin (*Geneva*) on "Rheumatoid Arthritis of the Aged", and by Prof. A. Lunedi (*Florence*) on "Two Types of Rheumatism following Scarlet Fever". The presentation of papers will be confined to members of the Society and specialists in rheumatology resident in Central Italy.

Registrations should be sent to the Secretary, Istituto di Semeiotica Medica, Università di Roma, not later than January 31, 1954.

SECOND INTERNATIONAL CONGRESS OF CARDIOLOGY, 1954

The Second International Congress of Cardiology is to be held in Washington, D.C., on September 12-15, 1954, and will be followed by the Annual Scientific Sessions of the American Heart Association.

The scientific sessions will include formal papers, panel discussions, clinical pathological conferences, and visits to medical centres in Washington and Bethesda. The programme will be printed in French, Spanish, and English, and immediate translation of some of the papers and discussions will be made in three languages.

A series of visits to at least twenty of the leading cardiac clinics in different parts of the U.S.A. and Canada has been arranged to follow the congress.

RESEARCH IN RHEUMATOLOGY

GREAT BRITAIN

William Marsden Travelling Professorship, 1953-54

Earlier this year Dr. Ernest T. D. Fletcher was awarded the William Marsden "Travelling Professorship", given annually to a Senior Member of the Consultant Staff of the Royal Free Hospital Group, to enable him to pursue some particular line of investigation.

Dr. Fletcher has chosen to survey the position held by the specialty of rheumatology in various parts of the world, in view of the recommendations made by the College of Physicians in their recent Committee report which advocates the recognition of rheumatology as a specialty within general medicine.

He will examine the relationship of general internal medicine to the specialty of rheumatology and will report on the attitude of various distinguished members of the profession to the specialty, and also to what extent laboratory work (especially histo-chemical and chemical procedures) has supported the concept of collagen disease and helped to clarify the present somewhat confused situation. Dr. Fletcher has already completed his tour of Europe, and will present his report on his return from America next year.

CANADA

Arthritis Research Grants, 1953-54

The Canad.an Arthritis and Rheumatism Association announced in September that the practice of awarding direct grants had been temporarily discontinued to enable a reserve fund for research to be built up. Applications were referred to the Department of National Health and Welfare: the following awards have been made:

Prof. James A. Dauphinee (*Toronto*): Metabolic and biochemical abnormalities in various forms of arthritis.

Prof. Sylvia Bensley (*Toronto*): Connective tissue changes in the rheumatic diseases.

Dr. Metro Ogryzlo (*Toronto*): Clinical and haematological effects of ACTH and cortisone in rheumatoid arthritis, disseminated lupus erythematosus and related disorders (continuation of a project begun in 1950).

Prof. R. H. More (*Queen's University*): Pathogenesis of the exudation of the progressive damage of the lesions of the rheumatic diseases.

Dr. John D. Keith (*Toronto*): ACTH and cortisone in rheumatic fever.

Prof. E. M. Watson (*Western Ontario*): Biochemistry of connective tissue in relation to disease.

Prof. Louis P. Dugal (*Quebec*): Influence of ascorbic acid used with ACTH and cortisone in arthritis.

Dr. Leopold A. Long (*Montreal*): Bone marrow in rheumatoid arthritis.

Prof. R. D. H. Heard (*Montreal*): Metabolism of progesterone and desoxycorticosterone with particular reference to their conversion to anti-arthritic adrenocorticosteroids of the cortisone series.

Drs L. G. Johnson and K. R. Mackenzie (*Royal Victoria Hospital*): Physiopathological mechanism in rheumatoid arthritis.

Prof. Hans Selye (*Montreal*): Influence of hormones on incidence and prevention of arthritis.

Prof. Eric Wittkower (*Montreal*): Medical, social, and psychological factors in the cause and treatment of rheumatoid arthritis.

Dr. De Guise Vaillancourt (*Montreal*): Role of hypercortinism in inflammatory phenomena observed in rheumatoid arthritis.

It is understood that certain additional projects originating in Saskatchewan and British Columbia are still under consideration by government authorities.

ITALY

Second Acqui Rheumatology Prize, 1954

The closing date for the sending in of entries for this international prize competition for an unpublished work on some aspect of rheumatic disease has been extended to February 28, 1954. Detailed information may be had from the Azienda Autonoma della Stazione di Cura, Acqui, Piedmont, Italy.

U.S.A.

George Washington University Arthritis Research Unit

It was announced on October 25, 1953, by the Professor of Medicine, Dr. Thomas McP. Brown, that a $12,000 grant for arthritis research has been awarded to the George Washington University by the Eugene and Agnes Meyer Foundation.

The grant will aid in equipping and operating a laboratory at the University Hospital for research into the basic mechanism and management of arthritis and the rheumatic diseases.

Dr. Brown will direct this research with the assistance of Dr. Ruth Wichelhausen, microbiologist, and Dr. Harold Clark, biochemist.

EMPIRE RHEUMATISM COUNCIL

At the autumn week-end course, held at the Arthur Stanley Institute, Middlesex Hospital, on November 13, 1953, a lecture was given by Dr. Otto Steinbrocker (*New York*) on "Recent American Work on Rheumatism", in place of that on "The Intervertebral Disk" by Dr. O. Savage, as mentioned in the September issue, vol. 12, p. 238.

LIGUE INTERNATIONALE CONTRE LE RHUMATISME

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WORLD CONFEDERATION FOR PHYSICAL THERAPY

FIRST INTERNATIONAL CONGRESS, LONDON, 1953

At the first international congress of physical therapy held at Westminster Hall, London, on September 7-12, 1953, lectures and demonstrations of particular interest to rheumatologists were given by the following:

DR. H. A. BURT (*London*): **The Physiotherapist and the Arthritic Patient** (with film).
DR. WALLACE GRAHAM (*Canada*): **Fibrositis and Non-Articular Rheumatism** (with slides).
MISS L. DYER (*South Africa*): **Hydrotherapy as an Integral Part of Physical Medicine** (film).
MISS V. BARCLAY (*Wolverhampton*): **Recreational Activities in Rehabilitation.**
DR. F. S. COOKSEY (*London*): **Medical Approach to the Resettlement of the Disabled.**
MR. P. H. ST. JOHN WILSON (*Ministry of Health, London*): **Industrial Rehabilitation of the Disabled** (followed by a film).

Visits to hospitals included some where the chief feature was the application of physical therapy to the rheumatic diseases.

Guy's Hospital (Treatment of intervertebral derangement by traction: Dr. E. J. Crisp).
King's College Hospital, London (Rehabilitation of the disabled housewife: Dr. F. S. Cooksey).
London Hospital (Modern methods of treatment for rheumatoid arthritis: Dr. W. S. Tegner).
Medical Rehabilitation Unit, R.A.F. Station, Chessington (Use of electronic apparatus: Sqn. Ldr. C. B. Wynn Parry).
Royal Free Hospital (Use of radio-active sodium in the investigation of physiotherapeutic procedures: Dr. W. St. J. Buckler).
St. Benedict's Hospital, Tooting (The middle-aged rheumatic patient with preventable deformities).
St. Pancras Hospital (Rehabilitation of the elderly patient: Lord Amulree).
St. Stephen's Hospital, Fulham (The rheumatic sufferer and his treatment by drugs and physical measures: Dr. F. Bach).
West London Hospital (Demonstration of the treatment of rheumatoid arthritis: Dr. W. S. C. Copeman; Demonstration of the treatment of osteo-arthritis and gout: Dr. O. Savage).
Arthur Stanley Institute, Middlesex Hospital (Treatment in the deep pool of patients suffering from various types of chronic rheumatic disease).
University College Hospital, London (Application of physical methods in various stages of rheumatoid arthritis, ankylosing spondylitis, frozen shoulder, and postural backache: Miss M. Turner and Miss J. Neville-Ness.)

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Chronic Constrictive Pericarditis and Rheumatic Heart Disease. KALTMAN, A. J., SCHWEDEL, J. B., and STRAUS, B. (1953). *Amer. Heart J.*, **45**, 201. 4 figs, 9 refs.

One of the most difficult problems in the diagnosis of chronic constrictive pericarditis arises when this condition is associated with rheumatic heart disease. In a series of eighteen cases of constrictive pericarditis seen at the Veterans Administration Hospital, Bronx, N.Y., and proven at operation or necropsy, a cause was clearly apparent in only three cases, namely, tuberculosis in two cases and the presence of a foreign body in one. Among the remainder, five cases were associated with rheumatic heart disease, and these cases are described in detail.

All five patients were men. Two were improved by pericardectomy, and had the physical signs of mitral and aortic valve lesions, although no history of rheumatism was obtained. The other three died without operation, and post-mortem examination showed a grossly thickened adherent pericardium causing constriction in all three cases, as well as rheumatic carditis with valvular lesions. All had considerable cardiac enlargement, obvious clinically, with greatly raised venous pressure, chronic pulmonary congestion, and increased pulse pressure, and two patients had ascites.

The authors do not consider that the constrictive pericarditis was necessarily rheumatic in origin. They point out, however, that a clinical diagnosis of constrictive pericarditis is not excluded by the coexistence of rheumatic heart disease, heart sounds of normal intensity, and considerable cardiac enlargement. *J. A. Cosh.*

Comparative Effects of 3-Hydroxy-2-phenylcinchoninic Acid (HPC) and Aspirin on the Acute Course of Rheumatic Fever and the Occurrence of Rheumatic Valvular Disease. CLARK, E. J., and HOUSER, H. B. (1953). *Amer. Heart J.*, **45**, 576. 4 figs, 6 refs.

This report from a U.S. Air Force hospital is based upon the findings in 68 cases of rheumatic fever in young men (average age just over 20 years), 34 of whom were treated with 3-hydroxy-2-phenylcinchoninic acid (HPC) and 34 with aspirin. HPC was given in a daily dose of 20 mg. per kg. body weight, in three equal parts at hourly intervals, and aspirin in a daily dose of 1 gr. per lb. (0·14 g. per kg.) body weight, with a maximum of 150 gr. (10 g.), for the first 48 hours, then two-thirds of this dose for 5 days, followed by one-half of the original dose for 5 weeks, 4-hrly doses being given at first and 6-hrly later. Both HPC and aspirin were given for 6 weeks. In addition, all patients were given 600,000 units penicillin in oil daily for the first 4 days, and then 1 g. sulphadiazine daily for the rest of the period of study. There were two cases of carditis in the group given HPC and six in the group given aspirin, and no difference was noted between them in the course of the acute disease or in the incidence of significant murmurs 14 to 17 months after treatment was started. There was no difference between the groups as a whole in the duration of the acute illness, but aspirin exerted a more favourable effect on the arthritis, fever, and erythrocyte sedimentation rate than HPC. Toxic symptoms (diarrhoea, abdominal cramps, nausea, and vomiting) occurred in sixteen of the patients treated with HPC, but in no case were these sufficiently severe to require withdrawal of the drug. "Salicylism of some degree" occurred in all patients treated with aspirin, and in one case treatment had to be stopped because of hypoprothrombinaemia. The final conclusion is drawn that "in the dosages employed in this study, aspirin appears to be preferable to HPC in the treatment of acute rheumatic fever". *William A. R. Thomson.*

Heredity and Rheumatic Fever. A Study of 462 Families ascertained by an Affected Child and 51 Families ascertained by an Affected Mother. STEVENSON, A. C., and CHEESEMAN, E. A. (1953). *Ann. Eugen. (Camb.)*, **17**, 177. 24 refs.

The familial history of rheumatic fever was studied at the Royal Belfast Hospital for Sick Children, the basis of the investigation being the case records of 462 patients (195 boys and 277 girls) attending the rheumatic clinic. A health visitor went to the home of each child at least

once and took a detailed family history. If a member of the family had a history suggesting rheumatic fever, he or she was examined and the relevant hospital records were studied. [These details are set out in full in an appendix.]

It was found that when neither parent was affected the proportion of brothers of the patient who also had rheumatic fever was eighteen out of 670 (3 per cent.), and of sisters 43 out of 652 (7 per cent.). When one parent was affected the proportions were six out of 132 (5 per cent.) and seventeen out of 110 (15 per cent.) respectively. Assuming random sampling of sibships the risk for the siblings, estimated by Haldane's method, was 8 per cent. with normal parents and 17 per cent. when one parent was affected. It is pointed out that these figures underestimate the total risk to the brothers and sisters, as many of these were still children; in 71 of the 188 affected parents and aunts the onset of the disease was after the age of 15. Only one of the ten surviving pairs of twins was monozygotic and in this pair both children were affected. In the nine dizygotic pairs the second twin was unaffected in each instance. Although the authors had no control series, the increased risk to the sibs where one parent was affected suggests that genetic factors to some extent control susceptibility to the disease. *C. O. Carter.*

Radiological Diagnosis of Rheumatic Pericardial Effusion. BESTERMAN, E. M. M., and THOMAS, G. T. (1953). *Brit. Heart J.*, **15**, 113. 4 figs, 19 refs.

The radiological signs in 23 episodes of rheumatic pericardial effusion have been investigated [at the Canadian Red Cross Memorial Hospital, Taplow, Bucks]. A sudden increase of cardiothoracic ratio and strengthening of the left border were the most consistent and the earliest signs of developing effusion. Change of contour, bulging of the right border, widening of the vascular pedicle, disappearance of the shadow of the descending aorta, and haziness of the posterior border in the oblique view were less consistent and usually later signs, but nevertheless useful ones. No constant change in the right cardio-diaphragmatic angle was observed.

A diminution in cardiothoracic ratio was the earliest radiological sign of resolution. Narrowing of the vascular pedicle, increased clarity of the posterior border in the oblique view, and return to normal of the right border followed later. Straightening of the left border and absence of the shadow of the descending aorta persisted longest, in some cases indefinitely.

The effect of posture on the shape of the heart shadow in pericardial effusion has been studied, particularly that of tilting head downwards to elicit the sign of divergent vascular shadows. This sign was found to be of limited value in the differentiation between effusion and cardiac enlargement.

Cases that had been diagnosed as having cardiac enlargement from established valve lesions were reviewed, and six of them were diagnosed in retrospect as having had effusions. Points that were of value in making this distinction are emphasized.

Cases with carditis have been reviewed to determine the incidence of rapidly progressive cardiac enlargement in the absence of pericarditis. It occurred in only nine out of 215 cases; all of them had established valve lesions and active rheumatism, and one had failure. Only in the one with failure was the rate of increase comparable to that which had been observed in pericardial effusion. Acute dilatation does not, therefore, seem to occur in early rheumatic carditis.

Seventeen cases with and without effusion have been catheterized. The value of the technique in differentiating between pericardial effusion and cardiac enlargement is emphasized.—[*Authors' summary.*]

Rheumatic Fever and Rheumatic Heart Disease. Their Occurrence in Helsinki. KALLIO, M. (1953). *Ann. Med. intern. Fenn.*, **42**, 199. 6 figs, 10 refs.

Aetiological Considerations and the Prevention of Rheumatic Fever. MACLEOD, C. M. (1953). *Maryland med. J.*, **2**, 236. 12 refs.

Studies on the Prevention of Rheumatic Fever: The Effect of Time of Initiation of Treatment of Streptococcal Infections on the Immune Response of the Host. BROCK, L. L., and SIEGEL, A. C. (1953). *J. clin. Invest.*, **32**, 630. 1 fig., 8 refs.

Antibody Production and Tuberculin Sensitivity in Individuals with a History of Rheumatic Fever. QUINN, R. W., SEASTONE, C. V., and DICKIE, H. A. (1953). *J. Immunol.*, **70**, 493. 3 refs.

Serum Electrolyte Balance in Normal Subjects and Patients with Rheumatic Fever treated with Large Doses of Congo Red. (La crasi elettrolitica sierica nel normale e nel reumatico acuto trattato con forti dosi di Rosso Congo.) PELLEGRINI, P., MASONI, A., and RUSSO, L. (1953). *Policlinico, Sez. prat.*, **60**, 1037. 13 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Familial Rheumatoid Arthritis. (Arthrite rhumatismale familiale.) STECHER, R. M., and HERSH, A. H. (1952). *J. Génét. hum.*, **1**, 191. 4 figs.

The pedigree is presented of a family in which three women—two cousins and an aunt—had rheumatoid arthritis. The fathers of the affected cousins were brothers of the affected aunt. The propositus had two sisters and a brother who survived to adult life and were all normal; her cousin had one normal brother, and her aunt had two sisters and two brothers, all unaffected. Full histories and clinical details of the condition in the two cousins, both of whom were examined by the authors at the City Hospital, Cleveland, Ohio, are given. The onset was at the ages of 29 and 28 years respectively, and was more insidious in the index case than in her cousin; both had severe pain, swelling, deformity, and eventually rigidity of the joints, with systemic symptoms and an elevated erythrocyte sedimentation rate. The aunt had already died, but from the nature of information elicited from the family and medical records she had evidently suffered from a similar type of severe chronic rheumatoid arthritis

leading to complete immobilization. The three affected individuals were stated to have lived in completely different environments.

The authors refer to another, unpublished, study which, they state, shows a familial pattern of rheumatoid arthritis to be consistent with transmission as an irregular dominant gene with 50 per cent. penetrance. It is suggested that the present work supports the hypothesis that a form of rheumatoid arthritis may be transmitted as a dominant gene with partially or completely sex-limited manifestation. *R. H. Cawley.*

Cardiac Lesions in Rheumatoid Arthritis. (Lesiones cardíacas en la artritis reumatoidea.) JOSELEVICH, M., and SUCARI, L. (1953). *Pren. méd. argent.*, **40**, 679. Bibl.

The authors begin by questioning the possibility of any aetiological relationship between rheumatic fever and rheumatoid arthritis, especially in view of reports in the recent literature on the cardiac complications of the latter condition. According to them, most European authorities believe they have a common aetiology, whereas most workers in North America (exceptions are mentioned by name) hold the opposite view. The pros and cons of each theory are discussed. One possibility is that the disease attacks the brain and heart in the younger age group, whereas in older subjects the joints bear the brunt. The incidence of cardiac lesions in rheumatoid arthritis as reported in the literature has varied from 2 per cent. to 63 per cent. In one controlled series, in which patients who were over 50 years of age or who had any "non-rheumatic" type of heart disease were ruled out, it was found that 35·8 per cent. of the remaining cases had some cardiac anomaly. It is obvious from these figures that very little agreement has been reached on this question.

The authors then describe six cases of rheumatoid arthritis and two of non-rheumatoid arthropathies, associated in all cases with heart disease, including one case of chronic cor pulmonale, another of calcified pericardium, and two of "chronic aortitis". In one case of gout there was an apical systolic murmur. From these cases it is concluded that rheumatoid arthritis may be complicated by cardiac disease of varied aetiology, and from this variation arises the difficulty of arriving at any definite conclusion.

[This must surely result when authors choose to base their conclusions on a total of eight patients of whom five were well over the age of 50; it must be obvious that the problem of this relationship cannot be solved by including degenerative cardiac lesions, and that far larger series and younger patients must be studied.] *Paul B. Woolley.*

Chronic Rheumatic (Rheumatoid) Diarthritis and the Shoulder-Hand Syndrome. KELLY, M. (1953). *Med. J. Aust.*, **1**, 330. 3 figs, 14 refs.

In a previous paper (*Med. J. Aust.*, 1952, **2**, 79) the author attempted to show that chronic rheumatic or rheumatoid monarthritis could not be clearly differentiated from rheumatoid polyarthritis. In the present paper he first points out that rheumatoid arthritis may persist for years in two joints without spreading to others, but that in rheumatoid diarthritis two unrelated joints are involved at the same time and, most commonly, either the neighbouring joint or the corresponding joint on the opposite side of the body is affected. The exception to this generalization is to be found in the shoulder-hand syndrome, the elbow being unaffected in this condition.

The author briefly describes fifteen cases of diarthritis to demonstrate that the arthritis may remain confined to the two joints, may subside, or may later spread to many joints. In his view the shoulder-hand syndrome, which was present in two of these cases, may be merely a stage during the onset of rheumatoid polyarthritis or a stage during remission. The swelling of the hand and stiffness of the fingers in this condition are usually secondary to arthritis of the wrist or of the metacarpo-phalangeal joints.

Infective arthritis (involving a few large joints) and true rheumatoid arthritis (with onset in the hands and toes and marked symmetry) cannot, in the author's view, be distinguished as separate entities. *C. E. Quin.*

Placental Blood Serum in the Treatment of Rheumatoid Arthritis. Preliminary Report. SPIELBERG, M. (1953). *Arch. intern. Med.*, **91**, 315. 10 refs.

A therapeutic trial of placental blood serum in the treatment of rheumatoid arthritis, based on the well-known beneficial effect of pregnancy, is here recorded. The placental blood was collected aseptically immediately after a birth, the amount obtained varying from 20 to 100 ml. Exact details are given of the preparation of a pooled and filtered serum, tested for sterility, and serologically for syphilis. No placental blood was taken from a mother who was Rh-negative, or who had a history of syphilis or a positive Wassermann reaction.

At the Arthritis Clinic, Jewish Hospital of Brooklyn, New York, fifteen female patients with rheumatoid arthritis were the subject of an adequately controlled study. Definite improvement was noted in ten patients, beginning as early as the second day in three cases, and in nine within the first week. The optimum effect of the treatment was obtained by giving 30 ml. placental serum intravenously daily for the first 2 weeks, 30 ml. three times a week for the next 2 weeks, then twice a week for 3 more weeks, and finally 30 ml. once a week for 1 to 3 weeks. The improvement observed included reduction of joint stiffness, of tenderness and swelling, of pain on movement, and of muscle spasm; improvement in muscle tone and mobility; increased sense of well-being, more restful sleep, improved appetite, and improved ability to carry out everyday duties. The microcytic hypochromic anaemia responded without other treatment. The erythrocyte sedimentation rate fell to normal in two cases.

The five patients who showed no response were all in the post-menopausal age group, and the duration of their disease varied from 6 to 31 years. Of the ten patients who improved, three had complete remission, three major improvement, and four minor improvement. One patient who had derived no benefit from cortisone, and two who had suffered toxic side-effects with cortisone, responded very well to placental blood serum. Administration of

the serum can be stopped without relapse. So far, improvement has been maintained for six months, but further observation is needed to determine its maximum duration; no toxic side-effects have been noted. It is considered that these results suggest that the active therapeutic principle is not cortisone or corticotrophin. Four case histories are recorded. *Kenneth Stone.*

Observations on Gold Therapy in Rheumatoid Arthritis. BROWN, R. A. P., and CURRIE, J. P. (1953). *Brit. med. J.*, **1**, 916. 17 refs.

Although many attempts have been made in the past 20 years to assess the value of gold in the treatment of rheumatoid arthritis, only a small proportion of the observations reported in the literature were made under strictly controlled conditions, and even then in many cases other remedial measures were in use at the same time. The results obtained vary widely, the most favourable reports claiming improvement in 80 per cent. of all cases treated with gold [a figure that appears unduly high; under the best conditions it is unlikely that more than 60 to 70 per cent. of any series of cases of rheumatoid arthritis would show improvement, while the "cure" rate would probably not exceed 10 per cent.].

In a further attempt to determine whether the benefits to be obtained from gold treatment are sufficient to offset the disadvantages of its toxic effects, the authors treated a series of 220 cases in the out-patients' department of the Glasgow Royal Infirmary over a period of 13 weeks, each patient receiving one of six different forms of treatment, namely:

(1) gold injections,
(2) copper ("cuprelone") injections,
(3) saline injections,
(4) arsenic (neo-arsphenamine) injections,
(5) aspirin by mouth, and
(6) physiotherapy.

The criteria for diagnosis and assessment of progress are defined. At the end of the course the proportion of cases improved both symptomatically and objectively was highest in the groups treated with gold and arsenic. These groups, however, consisted only of early and active cases, and when elderly patients and advanced cases were excluded from the other groups the difference in results was insignificant, both immediately and at the end of 12 months.

[These findings may be misleading, for it is the experience of those who have used gold over many years that the best results are rarely observed until after the second course, usually administered after an interval of 2 or 3 months, or even until after later courses given at similar intervals. Gold therapy is most effective if begun in the first year after the onset and in patients in early adult life, but only if the general health is satisfactory and the aetiological factors are controlled as far as possible—especially psychological influences. Physical methods may help greatly, especially gentle exercises carried out at home under instruction, but long-continued attendance at a physiotherapy clinic may have a bad psychological effect ultimately, as also may the advice of patients' friends. Such factors may easily neutralize the benefit which might have resulted from any therapeutic measures, and may account for the wide variations in the reported results of gold therapy.] *C. W. Buckley.*

Rheumatoid Arthritis: A System of Treatment. MARSHALL, C. M. (1953). *Med. J. Aust.*, **2**, 142. 4 refs.

Action of Cortisone and Corticotrophin (ACTH) in Rheumatoid Arthritis. (Accion de la cortisona y de la corticotropina (ACTH) en la artritis reumatoide.) LOSADA, M., and ZANARTU, J. (1953). *Rev. clin. esp.*, **49**, 383. 16 refs.

Lymph Nodes in Rheumatoid Arthritis before and after Treatment with ACTH. (Le ghiandole linfatiche nella poliartrite cronica prima e dopo somministrazione di ACTH.) MUCIO, G., and PEZONE, B. (1952). *Rass. Fisiopat. clin. ter.*, **24**, 1527. 9 figs, 30 refs.

Perforated Gastric Ulcer during Cortisone Therapy for Rheumatoid Arthritis. KERDASHA, R. (1953). *J. med. Soc. N.J.*, **50**, 343. 12 refs.

Errors and Prejudices in the Gold Treatment of Inflammatory Rheumatism. (Erreurs et préjugés dans la chrysothérapie des rhumatismes inflammatoires.) FORESTIER, J., and CALAIS, R. (1953). *Praxis*, **34**, 704.

Nitrogen Mustard in Rheumatoid Arthritis. (Mostaza nitrogenada en la artritis reumatoidea.) SPINDLER, S. (1953). *Pren. méd. argent.*, **40**, 1797.

Treatment of Rheumatoid Arthritis and Allied Conditions with the Cholinergic Drugs. COHEN, A. (1953). *Rheumatism*, **9**, 7. 1 fig., 12 refs.

Copper in the Treatment of Rheumatoid Arthritis. (Zur Kupfertherapie der chronischen Polyarthritis.) PRIBILLA, W., and MÜTING, L. (1953). *Ärztl. Wschr.*, **8**, 839. 21 refs.

Chrysotherapy and the Adrenal Cortex. (Chrysothérapie et cortex surrénalien essai d'interprétation.) ROSKAM, J., CAUWENBERGE, H. VAN, and VLIERS, M. (1953). *Rev. Rhum.*, **20**, 385. 6 figs, 10 refs.

Functional Training of the Hand in Rheumatoid Arthritis. BAKER, F. (1953). *Rheumatism*, **9**, 65. 4 figs, 3 refs.

Keeping the Patient with Rheumatoid Arthritis Employable. RAGAN, C. (1953). *Industr. Med. Surg.*, **22**, 309.

Clinical and Statistical Contribution to the Nosography of Rheumatoid Arthritis and its Variants. (Contributo clinico-statistico al nosografismo dell'artrite reumatoide e sue varietà.) CERVINI, C., and LONGO, C. (1953). *Policlinico, Sez. prat.*, **60**, 1041. 4 figs, bibl.

Effect of Puerperal Plasma in Rheumatoid Arthritis. (Influenza del plasma di puerpera nella poliartrite cronica primaria (Artrite reumatoide).) MARINOSCI, A., and SICILIANO, G. (1953). *Policlinico, Sez. prat.*, **60**, 1233. 17 refs.

Radiological Changes in Inflammatory Rheumatism. (Altérations radiologiques des rhumatismes inflammatoires.) JACQUELINE, F., FORESTIER, J., and FAIDHERBE, P. (1953). *Rhumatologie*, **4**, 222. 8 figs, 20 refs.

(Osteo-Arthritis)

Heberden's Nodes and Cervical Spondylarthrosis. [In English.] PELTOLA, P., and AHTO, A. (1953). *Ann. Med. intern. Fenn.*, **42**, 64. 2 figs, 16 refs.

At the Kivelä Hospital, Helsinki, the authors investigated the relationship between Heberden's nodes and a localized condition of osteo-arthritis, which, in some cases, had been observed in the region of the 5th to the 7th cervical vertebrae and which, they suspected, might have irritated or compressed the main nerve trunks supplying the hand. Radiological examination of the cervical spine in 207 patients with well-developed Heberden's nodes revealed osteo-arthritic changes in this region in more than 90 per cent. of patients in each age group over 40 years. In patients with nodes on the fingers of one hand only, the spondylarthrosis was confined to that side of the spine, and encroachment on the intervertebral foramina was clearly demonstrated.

W. S. C. Copeman.

Osteo-Arthritis of the Hip Joint. STONHAM, F. (1953). *Med. J. Aust.*, **1**, 916.

Experiences with the Muscle-Transplant Operation for the Relief of Painful Arthritis of the Hip. MEYERS, M. H. (1953). *J. Bone Jt Surg.*, **35A**, 384. 3 refs.

Keeping the Patient with Osteo-Arthritis Employable. HARTUNG, E. F. (1953). *Industr. Med. Surg.*, **22**, 312.

(Spondylitis)

Benign Form of Acute Osteitis of the Spine in Young Children. BREMNER, A. E., and NELIGAN, G. A. (1953). *Brit. med. J.*, **1**, 856. 6 figs, 6 refs.

A benign form of acute osteitis of the spine is described in this paper from the Royal Victoria Infirmary, Newcastle upon Tyne, and University of Durham, and seven cases in children aged 9 months to 2½ years are reported. The onset of symptoms was characteristically insidious, and there was often some delay before a correct diagnosis was reached. The initial symptoms were those of a febrile illness followed by stiffness of the back with pain. Commonly the patient objected strongly to sitting down and to physical examination. In four patients there was limitation of hip movements and a well-marked limp. Radiological evidence of narrowing of a disk space with osteoporosis and erosion of the adjacent vertebral bodies was found on admission in six cases and two weeks after admission in the seventh case. Treatment consisted in immobilization in a plaster bed for periods ranging from 7 to 22 months. All the children made a good recovery; in only one case was penicillin administered.

The author emphasizes the danger in these cases of diagnosing and treating the condition as tuberculous osteitis of the spine. The tuberculin skin test and radiological evidence of recalcification within 3 months of the onset of pyogenic osteitis are useful diagnostic aids.

J. S. Batchelor.

Ankylosing Spondylitis. [In English.] HART, F. D. (1953). *Schweiz. med. Wschr.*, **83**, 786. 9 refs.

Aetiology of Spondylolisthesis. (L'étiologie du spondylolisthésis.) BROCHER, J. E. W. (1953). *Schweiz. med. Wschr.*, **83**, 788. 4 figs, 7 refs.

Osteo-Cartilaginous Lesions of the Pelvis in Ankylosing Spondylitis. (Les réactions ostéo-cartilagineuses du bassin (sacroiliaques exceptées) dans la spondylarthrite ankylosante ou spondylose rhyzomélique.) FRANÇON, F., LAC, G. DU, JOLY, L., and FAIDHERBE, P. (1953). *Rhumatologie*, **4**, 195. 6 figs, 7 refs.

(Miscellaneous)

Effect of Vasodilating and Vasoconstricting Drugs on the Temperature of Normal and Arthritic Joints. HOLLANDER, J. L., and HORVATH, S. M. (1953). *Arch. phys. Med.*, **34**, 162. 2 figs, 6 refs.

It has been shown that the intra-articular temperature of a joint is a more accurate index of arthritic activity than the skin temperature, and that a reciprocal reflex exists between the blood flow of the skin and deep tissues. In previous work the authors studied the effect of disease, physiotherapy, administration of cortisone, and intra-articular injection of hydrocortisone on the synovial circulation, and in the present paper, from the University of Pennsylvania, they report their observations on the effect of vasodilator and vasoconstrictor drugs.

To measure the intra-articular temperature a plastic catheter thermocouple was introduced into the joint through an aspiration needle, the patient being at rest in a room at 22° ± 1° C. The skin and joint temperatures were recorded before and after the administration of various drugs, several joints, some normal and some arthritic, being studied in the same patient. The vasodilator drugs were procaine given by intra-articular injection, acetylsalicylic acid by mouth, nitroglycerin sublingually, and "Priscoline" (benzazoline), tetraethylammonium, and "Niacin" (nicotinic acid) intravenously. The vasoconstrictor drugs were adrenaline, phenylephrine, and posterior pituitary extract ("Pituitrin"), given intravenously.

The temperature of the inflamed joint did not rise markedly in any experiment, though there was a rise in the intra-articular temperature in normal joints following administration of the vasodilator drugs. This temperature change was inversely related to the arthritic activity of the joint. The vasoconstrictor drugs caused a fall in temperature in an inflamed joint, but, the authors state, the synovial circulation was not affected.

It is suggested that these experiments show that the synovial circulation in a diseased joint is a maximum,

and cannot be modified by the administration of vasomotor drugs. The effectiveness of physiotherapy, alone or in conjunction with hormone therapy, in altering the intra-articular temperature is stressed. *J. B. Millard.*

Tissue Therapy in Rheumatology. (La thérapeutique tissulaire en rhumatologie. (Implantation d'amnios et injections d'extraits placentaires.) Résultats de nos premiers essais.) SÈZE, S. DE, DURIEU, J., and CARLIER, J. C. (1953). *Bull. Soc. méd. Hôp. Paris*, **69**, 152.

The therapeutic use of preserved tissue grafts is based on the work of Filatov and other ophthalmologists. Although the effect of such grafts is non-specific, the authors decided to try them at the Hôpital Lariboisière, Paris, in the treatment of rheumatic affections such as rheumatoid and osteo-arthritis and ankylosing spondylitis. Experience soon showed the superiority of implants of amniotic tissue over placental tissue. Inserts were made at intervals of 2 weeks, generally in the subcutaneous tissue of the thigh, but occasionally in the region of the affected joint; six inserts in all were given, the course of treatment thus lasting 3 months. In addition, placental extract was given by injection or as a suppository on alternate days.

Altogether, 31 cases were treated and 210 implants made; abscess formation, with extrusion of the implant, occurred on only one occasion. All patients appeared to benefit from the treatment, but improvement was also noted in non-rheumatic affections such as chronic varicose ulceration and arteritis. The universal nature of the remedy must inevitably raise doubts about its value, but the authors are prepared to accept its possibilities as a "biostimulant". Nevertheless, in their view it cannot replace older remedies, such as gold or hormones, though it may be of value in conjunction with them. But in such a combination, as the authors remark, it would be even more difficult to determine the precise part played by these implants. *D. Preiskel.*

Operative Treatment of Chronic Osteomyelitis using Preserved Cartilage for filling the Bone Cavity. (Закрытый метод оперативного лечения хронического остеомиэлита применением консервированного хряща для заполнения операционной костной полости.) FEDOTENKOV, A. G. (1952). *Khirurgiya*, 57. 7 figs.

In experiments on dogs, cavities in bones were filled with small pieces of preserved cartilage and the wound closed up, with very good results. Histological examination 10 days to 14 months after the operation showed that in all cases the cartilage was slowly replaced by new formed bone; there was no difference in histological appearances whether homogeneous or heterogeneous cartilage was used. For the treatment of the cavities of chronic osteomyelitis in human patients cartilage removed from the cadaver and stored up to 3 months in a solution containing sugars and sulphonamides was used. Out of 26 cases, 23 were of haematogenous osteomyelitis and three were secondary to gun-shot wounds. In five cases the duration of the osteomyelitis was less than 5 years, and in 21 between 5 and 15 years; fifteen patients had been operated upon previously by other surgeons. After the excision of all diseased tissues the bone cavity was tightly packed with small pieces of cartilage (50 to 100 g. according to the size of the cavity), the skin and other soft tissues carefully stitched together, and the limb put in plaster for 2 weeks. General treatment with blood transfusions and antibiotics was carried out before, during, and after operation. In all 26 cases the wound healed up with no complications, and *x*-ray examination showed that the cavities were filled with new-grown bone 12 to 16 months after the operation. In ten cases observation lasted 1 to 2 years, and in none was there a relapse, nor in the remaining cases in which the period of observation was less than 1 year in duration. During the same period fifteen other cases were treated by a similar technique, but the cavities were filled up with a blood clot instead of cartilage. In this series, on removal of the plaster, only in seven cases had the wound healed; in the remaining eight cases the wounds were suppurating and the edges of the incision were gaping. After 2 years of observation there had been a relapse of osteomyelitis in five of these cases. The author is now investigating the use of heterogeneous cartilage for this type of operation. *P. T. Sander.*

Coccidioidomycosis of Bone in Children. DYKES, J., SEGESMAN, J. K., and BIRSNER, J. W. (1953). *Amer. J. Dis. Child.*, **85**, 34. 7 figs, 3 refs.

Coccidioidomycosis of bone was seen in 26 cases in children. The lesion is osteolytic in type, similar to that found in adults, and may occur as a single lesion or multiple lesions. It may or may not have an accompanying pulmonary lesion or cutaneous abscess. As a rule, the process is chronic, with relatively good prognosis for eventual recovery. Parenchymal infiltration of the lung frequently precedes the bone lesion, and at the time of osseous coccidioidomycosis there may be only residual pulmonary adenopathy. In endemic areas the lesion is not uncommon, and elsewhere it may occur frequently enough that coccidioidomycosis should be considered when there are osteolytic lesions in children. An appropriate travel and previous residence history may suggest this diagnosis.—[*Authors' summary.*]

Periarteritis Nodosa in a Child. (Случай уэелкового периартериита в детском воэрасте.) VOIT, E. B., and DENISOVA, N. A. (1953). *Pediatrija*, **1**, 62. 4 figs.

A boy, aged 12, was admitted to hospital after a fall while skiing, the diagnosis on admission being concussion and injury to the hip-joint. The patient's condition is described in detail. Before the accident he suffered from general debility, fatigue, headaches, and night sweats; while in hospital his condition gradually deteriorated and eventually a clinical diagnosis of acute nephritis with cardiac decompensation was made. The boy died 38 days after admission.

The pathological condition of the heart, liver, and kidneys was confirmed at necropsy, and is described. Histological examination revealed multiple affections of the muscular layers of the small and medium-calibre arteries in the kidneys, liver, gall-bladder, pancreas,

intestines, and heart. A diagnosis of periarteritis nodosa with definite characteristic changes in the arteries and the vasa vasorum was made. In addition, there was dilatation of the heart and hypertrophy of the left ventricle, bilateral pneumonia, partial obliteration of the pleural cavity, acute hyperplasia of the spleen with fibrosis of the capsule, and punctate haemorrhages in the mucous membranes and on the skin of the abdomen and chest.

The authors describe three further cases of nodular periarteritis in children (aged 10, 11, and 6 years) admitted to the hospital between 1941 and 1950, and review many other cases of periarteritis reported in the Russian literature, on which they make their own observations and comments. *H. W. Swann.*

Effect of "Butazolidin" on the Excretion of Water and Electrolytes. GREEN, J., and WILLIAMS, P. O. (1953). *Lancet*, **1**, 575. 2 figs, 5 refs.

Preliminary tests at the Royal Free Hospital, London, on rheumatic patients and on a healthy volunteer given 5 g. sodium chloride each day indicated that intramuscular injection of 1 g. "Butazolidin" (phenylbutazone) caused a fall in urine output, a big fall in urinary concentration of sodium within 4 hours, and retention of sodium chloride. More precise observations were made on four healthy volunteers fed on a diet poor in sodium and potassium and given, every 2 hours, 250 ml. water, 1 g. sodium chloride, and 0·2 g. potassium chloride, their total intake being about 9 g. NaCl and 4 g. KCl daily. After one day for stabilization, the amounts of water, sodium, potassium, chloride, and urea excreted in the urine were compared on two successive days, 1 g. phenylbutazone being injected intramuscularly on the 2nd day in three subjects. The 4th was not given phenylbutazone and served as a control. Blood and urine sodium and potassium concentrations were measured with a flame photometer.

Comparison of the total excretion between 10.30 a.m. and 10.30 p.m. before and after administration of phenylbutazone showed an average retention of 766 ml. water, 2·4 g. sodium, 0·4 g. potassium, and 3·56 g. chloride. From the figures for 2-hrly specimens of urine it is clear that after the administration of phenylbutazone, urine output falls within 2 hours and remains low for 24 hours. Urinary potassium concentration was increased about threefold, while sodium concentration remained steady in one subject and fell by one-half in the other two subjects. Urea output remained virtually unchanged.

It appears that phenylbutazone has a selective effect on the excretion of electrolytes and water, probably owing to increased reabsorption of sodium. The similarity to the action of salt-conserving adrenal hormones is noted, and it is suggested that if oedema occurs during treatment with phenylbutazone the intake of sodium should be restricted and mercurial diuretics should be given a trial. *Derek R. Wood.*

Effect of "Butazolidin" (Phenylbutazone) on Water and Electrolyte Excretion. WILKINSON, E. L., and BROWN, H. (1953). *Amer. J. med. Sci.*, **225**, 153. 5 figs, 10 refs.

Studies of the water and electrolyte excretion in four patients receiving "Butazolidin" (phenylbutazone) are here described from Salt Lake County General Hospital (University of Utah). In the first case a 55-year-old woman with chronic rheumatoid arthritis of about 20 years' duration, under treatment in her own home, was given butazolidin, 0·2 g. three times a day, without regard to salt intake. Five days later, the patient developed severe pulmonary oedema. The administration of "butazolidin" was subsequently resumed, after her admission to hospital, at the same dosage but with a salt-poor diet containing about 2 g. sodium chloride per day. Within 6 days, the patient gained weight, and the addition of further quantities of sodium chloride to the diet resulted in a further rapid increase in weight. With the discontinuance of the drug, the institution of a salt-poor diet, and the administration of one injection of a mercurial diuretic (mercuhydrin), there was a marked sodium, chloride, and water diuresis, and her weight returned to normal.

In the second case treatment of a man of 52 with "Butazolidin" resulted in a gain of weight. When the drug was withdrawn, a sodium and chloride diuresis took place and a loss of body weight was recorded, but renewal of the treatment again caused a steady increase in weight and a decrease in urine volume and sodium and chloride excretion. In the third patient, a 28-year-old male with rheumatic fever, the administration of butazolidin also resulted in an increase in weight and diminution of urine volume and sodium and chloride excretion.

The fourth patient was a 56-year-old female who had chronic rheumatoid arthritis, diabetes, and obesity. "Butazolidin" treatment and a salt-poor diet resulted in four days in a gain of weight and the development of peripheral oedema. The drug was stopped, and diuresis was induced with a mercurial diuretic. The glomerular filtration rate, as measured by endogenous creatinine clearance, was unchanged, so that the decreased excretion was probably due to increased tubular reabsorption.

It is pointed out that with the increased use of butazolidin as an anti-rheumatic agent, the potential hazards of the drug should be recognized. In most patients fluid retention is not a serious complication, but in patients subject to this development, butazolidin therapy appears to be hazardous if proper precautions, such as a low-salt diet and the giving of mercurial diuretics, are not employed. *G. B. West.*

Study of the Therapeutic Efficacy of Phenylbutazone ("Butazolidin"). (Estudio sobre la efectividad de butazolidina.) BARCELÓ, P., and SERRA-PERALBA, A. (1953). *Med. clin. Barcelona*, **20**, 152. 3 figs, 23 refs.

At the University Medical Clinic, Barcelona, 25 patients with rheumatoid arthritis were treated with phenylbutazone given orally or by injection. The results were good, fourteen patients obtaining complete and seven partial relief. The beneficial effect was apparent within 3 hours, and the drug appeared to act by damping down the inflammatory process rather than solely by virtue of its analgesic properties. Its action also appeared to be more prolonged than that of cortisone. Severe toxic effects were not encountered in this small series of cases, but malaise, skin rashes, epigastric pain, and buccal

ulcers were noted. The authors conclude that phenylbutazone is a valuable drug for the treatment of the acute phases of rheumatoid arthritis. *K. Gurling.*

Treatment of Rheumatism with "Butazolidin" (Phenylbutazone). (Rheumatherapie mit Butazolidin.) RECHENBERG, H. K. VON (1953). *Schweiz. med. Wschr.*, **83**, 159. 4 figs, 12 refs.

At the Cantonal Hospital, St. Gallen, Switzerland, the authors have used "Butazolidin" (phenylbutazone) in the treatment of 125 cases of various "rheumatic" affections, such as acute polyarthritis, subacute and chronic polyarthritis, osteoarthritis, arthralgias of other kinds, periarthritis, lumbago, sciatica, and trigeminal and other neuralgias. A high proportion of these patients were benefited by this treatment; the improvement in cases of acute polyarthritis was the most dramatic, twelve of fifteen cases showing marked improvement and three showing considerable improvement. In the whole series 23 patients were greatly improved, 55 moderately improved, thirty slightly improved, and seventeen derived no benefit.

Antipyretic and antiphlogistic effects were found to be more marked than the analgesic properties of the drug. Butazolidin alone, the author concludes, is as good an antirheumatic agent as either "Dipyrin" or "Irgapyrin", and in addition the well-known toxic effects of the pyrazole bodies occurred more rarely than with the other two drugs. In particular, no cases of agranulocytosis occurred in the 125 cases treated. The recommended dosage is two tablets of 0·25 g. each three times a day, followed after a few days by one tablet three times a day for 1 or 2 weeks. Treatment can also be given per rectum, and the dosage then is one suppository of 0·25 g. twice daily, later reduced to one suppository daily for another week.

Marianna Clark.

"Butazolidin" in Rheumatic Disorders. (La butazolidine dans les affections rhumatismales.) SÈZE, S. DE, and LEVERNIEUX, J. (1953). *Rev. Rhum.*, **20**, 6.

The authors describe the treatment of 150 cases of various rheumatic disorders by the intravenous or intramuscular injection of "Butazolidin" (phenylbutazone). They found that the best results were obtained in cases of gout and ankylosing spondylitis. Cases of rheumatoid arthritis in men responded well, but the drug was less effective in women. In cases of low back pain, periarthritis of the shoulder, brachial neuralgia, and similar conditions the effects of treatment varied considerably but was effective in some cases.

The authors consider that phenylbutazone was more effective intravenously than when given intramuscularly, and found that very slow injection with the addition of 0·5 ml. of heparin helped to prevent thrombosis of the vein. Intramuscular injection was painful and sometimes led to abscess formation. It is stressed that butazolidin does not replace cortisone or ACTH in any way, but is effective in relieving pain in a number of conditions. It is suggested that butazolidin is more than an analgesic, since during its administration joint swelling subsided and range of movement increased. *Kathleen M. Lawther.*

Plastic Reconstruction of the Hip with Nylon. CHARRY, R. (1953). *J. int. Coll. Surg.*, **19**, 1. 27 figs.

A technique of arthroplasty is described in which, after remodelling of the femoral head and acetabulum has been carried out, the head is closely invested with a nylon film 0·5 mm. in thickness. It is claimed that the operation is suitable for many varieties of degenerative hip disease, and particularly for the late arthritis of congenital subluxation, where a simultaneous shelf operation is often advisable. *A. David Le Vay.*

Nylon Prosthesis in Lesions of the Shoulder, Elbow, and Finger. MACAUSLAND, W. R. (1953). *Amer. J. Surg.*, **85**, 164. 15 figs, 10 refs.

The author refers to the difficulty of regaining shoulder movement after a comminuted fracture of the upper end of the humerus, and describes two cases in which a prosthesis was used to replace the excised humeral head. In the first case a Judet acrylic femoral head was employed, but in the second a model of the humeral head was made of nylon, with provision for attachment of the musculo-tendineous cuff and tendons, and was inserted into the upper end of the humerus. The results were encouraging, and in another case a similar appliance was used to replace the lower end of the humerus, with an excellent result. A good result was also obtained by replacement of the head of the metacarpal of the index finger with a nylon prosthesis. *Dennis Walker.*

Relationship between Reiter's Syndrome and Gonorrhoea, reflected in some Cutaneous Symptoms. [In Swedish.] RUIKKA, I. (1953). *Nord. Med.*, **50**, 976. 33 refs.

Report of a case of atypical Reiter's syndrome in a female with conjunctivitis and keratoderma. The pathogenic relationship to infection with gonococcus is discussed. *E. Godtfredsen.*

A Study of 23 Cases of Reiter's Syndrome. HALL, W. H., and FINEGOLD, S. (1953). *Ann. int. Med.*, **38**, 533.

In the 23 cases reported, ocular involvement was restricted in the main to a mild or moderate bilateral conjunctivitis. The authors present evidence which suggests that the disease may be due to a venereal infection.

J. R. Hudson.

Rheumatism in the Shoulder. (Les rhumatismes de l'épaule.) SÈZE, S. DE, DEBEYRE, J., and DENIS, A. (1953). *Sem. Hôp. Paris*, **29**, 1855. 29 figs, 1 ref.

Chronic Lung Diseases and Rheumatism. (Pneumopathies chroniques et rhumatisme.) MARTIN, E., and FALLET, G. H. (1953). *Schweiz. med. Wschr.*, **83**, 776. 9 figs, 28 refs.

Onset of Various Rheumatic Diseases of the Locomotor System—a Study of Age Incidence in Rheumatism. (Über Erstmanifestation verschiedener rheumatischer Erkrankungen des Bewegungsapparates ein Beitrag zur Alterdisposition des Rheumatismus.) SEIDEL, K. (1953). *Z. Altersforsch.*, **7**, 140. 9 figs, 46 refs.

Observations on the Rheumatic Aetiology of Chronic Progressive Deafness without Local Cause. (Quelques remarques sur l'étiologie rhumatismale des surdités chroniques progressives sans cause locale.) MARCHAND, J. (1953). *Ann. Oto-laryng.* (*Paris*), **70**, 320. 1 ref.

Relaxation of Muscle Spasm in Chronic Arthritis by Prostigmin. HOWELL, T. H. (1953). *Brit. J. Phys. Med.*, **16**, 192. 1 ref.

Preliminary Study of the Morphogram in Chronic Rheumatism. (Einleitende Untersuchung des Morphogramms bei chronischen Rheumatikern.) COSTE, F., PIGUET, B., and BETOURNE, C. (1953). *Z. Rheumaforsch.*, **12**, 1. 1 fig., 7 refs.

Orthopaedic Aspects of Chronic Arthritis. SACKS, S. (1953). *S. Afr. med. J.*, **27**, 525.

Pseudo-Sciatica caused by Brucellosis. GISPERT CRUZ, I. DE, and ESCARPENTER, G. J. (1953). *Rheumatism*, **9**, 34. 20 refs.

Ocular Manifestations of Chronic Rheumatism in Children. Still's Disease. Ankylosing and Deforming Rheumatism. (Les manifestations oculaires dans les rhumatismes chroniques de l'enfance. Maladie de Still. Rhumatisme ankylosant et déformant.) BONNET, P., and BONNET, I. (1953). *J. Méd. Lyon*, **34**, 533.

Proposed Method for the Graphic Representation of the Objective Findings in Rheumatism. (Proposta per una rappresentazione grafica dell'obbiettività reumatica.) BALLABIO, C. B. (1953). *Reumatismo*, **5**, 268. 2 figs.

"Butazolidin" in the Treatment of Arthritis. Clinical Studies with Phenylbutazone. STRAZZA, J. A., and RESSETAR, M. (1953). *J. med. Soc. N.J.*, **50**, 333. 3 figs, 1 ref.

Indications for and Routes of Administration of Phenylbutazone ("Butazolidin"), with particular reference to Rheumatic Disease. (Sulle indicazioni e su alcune modalità di impiego del fenilbutazone (Butazolidina), con particolare riguardo alla malattia reumatica.) RATTI, G., PASARGIKLIAN, E., and BALLABIO, C. B. (1953). *Reumatismo*, **5**, 231. 7 figs, 43 refs.

Action of 2-Phenylquinolino-3-hydroxy-4-carbonic Acid in Rheumatic Disease. (Sull'azione dell'acido 2-fenilchinolin-3-idrossi-4-carbonico in malattie reumatiche. Ricerche sperimentali e cliniche.) SOLARI, S., and CURZIO, A. (1953). *Reumatismo*, **5**, 242. 1 fig., 16 refs.

Dosage of Sanocrysin in Arthritis and Tuberculosis. [In English.] SECHER, K. (1953). *Acta med. scand.*, **146**, 350. 10 figs, 21 refs.

Preliminary Trials of a Combination of Ethyl Morrhuate and Calcium Gluconate: its Rheumatological Applications. (Premiers essais de l'association "complexe morrhuate d'éthyle-gluconate de calcium": son intéret en rhumatologie.) ROZIER, M., and MOORLEGHEM, G. VAN (1953). *Rhumatologie*, **4**, 268. 1 ref.

Specificity of Treatment in the Various Forms of Inflammatory Rheumatism. (Spécificité de la thérapeutique dans les divers rhumatismes inflammatoires.) ROSKAM, J., and CAUWENBERGE, H. VAN (1953). *Schweiz. med. Wschr.*, **83**, 802. 1 fig., 15 refs.

Researches into the Mode of Action of Sodium Salicylate in the Treatment of Rheumatism. (Ricerche sul meccanismo d'azione del Na salicilato nella terapia antireumatica.) PELLEGRINI, U., and SALA, I. (1953). *Pediatria* (*Napoli*), **61**, 351. 34 refs.

Medical Recording of the Rheumatic Diseases. FRANCO, S. C. (1953). *Industr. med. Surg.*, **22**, 321.

Medico-Social Problem of Rheumatism in Brazil. (Problema médico-social do reumatismo no Brazil.) HOULI, J., and VELLOSO, G. D. (1953). *Hospital* (*Rio de J.*), **43**, 823. Bibl.

Emotional Factors in Rheumatic Disease. (Fattori emotivi nel decorso delle malattie reumatiche.) ANTONELLI, F. (1953). *Minerva med.* (*Torino*), **44**, 475. 12 refs.

Disk Syndrome

Quantitative Test for Prolapsed Disk. (Ein quantitativer Bandscheiben-Test.) KRON, R. (1953). *Z. Rheumaforsch.*, **12**, 140. 1 ref.

Intervertebral Disk Lesions from the Surgical Viewpoint. (Die Bandscheibenschäden vom chirurgischen Standpunkt.) BLUMENSAAT-BOTTROP, C. (1953). *Z. Rheumaforsch.*, **12**, 8. Bibl.

Manipulation of the Spine. EWER, E. G. (1953). *J. Bone Jt Surg.*, **35-A**, 347. 9 figs, 5 refs.

Keeping the Patient with Low Back Pain Employable. THOMPSON, W. A. L. (1953). *Industr. Med. Surg.*, **22**, 318. 2 figs.

Gout

Keeping the Patient with Gout Employable. GUTMAN, A. B. (1953). *Industr. Med. Surg.*, **22**, 311.

Non-Articular Rheumatism

The Patient with Extra-Articular Rheumatism. FREYBERG, R. H. (1953). *Industr. Med. Surg.*, **22**, 316.

Keeping the Patient with Shoulder Syndrome Employable. STEINBROCKER, O. (1953). *Industr. Med. Surg.*, **22**, 314.

Peri-Arthritis of the Hip. (Péri-arthrites de la hanche.) GRABER-DUVERNAY, J. (1953). *Rhumatologia*, **4**, 217.

General Pathology

Lymph Nodes in Rheumatoid Arthritis. MOTULSKY, A. G., WEINBERG, S., SAPHIR, O., and ROSENBERG, E. (1952). *Arch. intern. Med.*, **90**, 660. 5 figs, 33 refs.

Because examination of lymph-node biopsy specimens from patients with rheumatoid arthritis occasionally revealed lesions thought to resemble giant follicular hyperplasia (Brill-Symmers disease), lymphosarcoma, or Hodgkin's disease, a study of the appearances of enlarged

lymph nodes in nine patients with rheumatoid arthritis was undertaken at the Michael Reese Hospital, Chicago. In six patients there were features interpreted initially as indicating giant follicular hyperplasia, early lymphosarcoma, or Hodgkin's disease; in another patient there was complicating infectious mononucleosis, and at a later date pyoderma. *X*-ray therapy had been given to six patients and nitrogen mustard treatment to another, resulting in some little improvement in the arthritis for a short time and decrease in size of lymph nodes. In a review of the cases, fusion of follicles was found in four, compression of lymphatic sinuses in six, infiltration of capsule with lymphocytes in six, and follicular hyperplasia in eight.

It was finally decided that all the specimens examined showed a reactive hyperplasia. Histologically, the differential diagnosis between reactive hyperplasia and Brill-Symmers disease rests upon the generalized distribution of follicles and their large size and increased number in the latter disease. There is also compression of the sinuses and of the interfollicular tissues, but phagocytosis and proliferation of reticulo-endothelial cells are absent.

There follows a general review of the literature dealing with lymph-node changes in rheumatoid arthritis, with particular reference to hyperplastic conditions and this, together with their own cases, leads the authors to suggest that a wider knowledge of this spurious "lymphomatous" picture would lead to less discomfort for the patient, both with regard to the prognosis he is given and the irradiation treatment he undergoes. *E. G. L. Bywaters.*

Rheumatoid Arthritis and the Liver. [In English.] LÖVGREN, O. (1953). *Ann. Med. intern. Fenn.*, **42**, 42. 14 refs.

In view of the fact that when acute hepatitis supervenes in rheumatoid arthritis there is often relief of joint pain, a special study has been made, at St. Erik's Hospital, Stockholm, of the connexion between disordered hepatic function and rheumatoid arthritis. The author had previously drawn attention to the low serum iron and citric acid levels in rheumatoid arthritis, and he later found that in acute hepatitis the exact opposite prevailed. This led him to suspect some physiological antagonism between the two disease conditions, the cause of which might be found in the liver.

The hippuric acid test was carried out in thirty patients with rheumatoid arthritis, and in ten evidence of gross liver damage was found. The results of the phosphatase test were negative in all the patients, while the thymol reaction was positive in over half of them. Of 93 cases of rheumatoid arthritis seen *post mortem*, liver damage was found in 52, and histological changes of a pathological nature were found in seven of thirteen patients on whom liver biopsy was performed. *W. S. C. Copeman.*

Toxic Reactions due to Intravenous Iron. LIBRACH, I. M. (1953). *Brit. med. J.*, **1**, 21. 29 refs.

The reactions of two patients with active tuberculosis to the intravenous injection of a proprietary preparation of iron are described. One patient had a convulsion within one minute but rapidly recovered; subsequent intravenous injections of another preparation were followed by a mild general reaction. The second patient, an asthmatic, developed dyspnoea and cyanosis, for which adrenaline had to be given. She received a number of intravenous injections subsequently, the reaction depending on the size of the dose, the most severe reaction occurring after a dose of 100 mg. or more.

The possible causes of the reactions are discussed at considerable length. *J. M. Barnes.*

Contributions to the Pathogenesis of Acute Rheumatism. I. The Significance of Disturbances of Permeability. (Beiträge zur Pathogenese des akuten Rheumatismus. I. Die Bedeutung der Permeabilitätsstörung.) ECKERT, H., GLEISS, J., and KÜSTER, F. (1953). *Z. Kinderheilk.*, **72**, 452. 2 figs, 22 refs.

Frontali (1950) reported that in patients with acute rheumatism he had found an anatomical abnormality of the capillaries and an impairment of their resistance, affecting probably the whole body, and persisting often for years after the acute rheumatic episode. He postulated an abnormal endothelial constitution as the basis for the tendency to rheumatic fever. In order to shed more light on this problem the authors examined the capillary resistance of 24 children with acute rheumatism at the Medical Academy, Düsseldorf. They used the method of applying negative pressure to the skin of the infraclavicular region; in seven cases they used in addition the method described by Landis (*Amer. J. med. Sci.*, 1937, **193**, 297), which consists in applying a pressure of 40 mm. Hg for half an hour to the arm, and then drawing off blood from the area of venous stasis. By means of a haematocrit the amount of serum lost through transudation from a given volume of blood is estimated. Plasma proteins are estimated by colorimetry, and from the haematocrit reading and plasma protein level the amount of protein which has escaped through the capillary walls into surrounding tissues can be calculated.

In normal subjects the test should cause little or no transudation of serum and no passage of plasma proteins through the capillary walls. In six of the seven cases in which the method of Landis was used the test result was strongly positive, with considerable escape of proteins. The only negative result, however, occurred in a child who was severely ill, and who showed normal or even increased capillary resistance in response to the negative-pressure test.

The authors therefore confirmed that, as a rule, capillary resistance is diminished in cases of rheumatic fever. They found, however, that the resistance may go on decreasing even though there is a good clinical response to treatment with amidopyrine, and that the degree of impairment of capillary resistance is not correlated with the severity of the disease. Its estimation is therefore of no prognostic value. They conclude that their experiments show that disturbance of capillary function is undoubtedly a factor in the pathogenesis of acute rheumatic fever, but that it does not, by itself, offer a satisfactory explanation of the tissue damage present in rheumatism. *Marianna Clark.*

Iron Metabolism: Clinical Evaluation of Iron Stores. STEVENS, A. R., COLEMAN, D. H., and FINCH, C. A. (1953). *Ann. intern. Med.*, **38**, 199. 3 figs, 5 refs.

The authors assessed the significance of the amount of haemosiderin contained in the sternal marrow of 298 patients at the King County Hospital, Seattle, Washington. The specimen, obtained in the usual manner, was mixed with sodium citrate, and smears were made from marrow particles. The haemosiderin granules could be seen without staining under an oil-immersion lens, and with practice a special stain was unnecessary.

The amount of haemosiderin in the marrow of women was found to be less than that in the marrow of men in all conditions except iron-deficiency anaemia, when it was generally absent in both sexes. The authors claim that by the use of this technique it is possible to assess the need for therapy, as only those patients with marked reduction or absence of storage iron are likely to respond to iron; and that it is particularly useful in the anaemia of infection, which is often associated with a low serum iron level but in which there are ample iron reserves, so that the condition does not need treatment with iron compounds.

[The conclusions reached by the authors agree with those of workers in this country and confirm that the estimation of iron content should be an essential part of the marrow examination.] *R. F. Jennison.*

Specific Inhibitor for Human Desoxyribonuclease and an Inhibitor of the Lupus Erythematosus Cell Phenomenon from Leucocytes. KURNICK, N. B., SCHWARTZ, L. I., PARISER, S., and LEE, S. L. (1953). *J. clin. Invest.*, **32** 193. 6 figs, 27 refs.

In experiments performed at Tulane University School of Medicine, New Orleans, extracts of leucocytes which had been disintegrated by freezing and thawing were shown to contain an inhibitor for human desoxyribose nuclease. The authors investigated the chemical nature of this factor and found it to be a relatively stable protein. Its properties were very similar to those of the inhibitor of the "L.E.-cell" phenomenon previously demonstrated in leucocytes, and the authors suggest that these two inhibitors are identical. *Marjorie Le Vay.*

Study of the Erythrocyte Sedimentation Rate for Well Children. HOLLINGER, N. F., and ROBINSON, S. J. (1953). *J. Pediat.*, **42**, 304. 2 figs, bibl.

Although the erythrocyte sedimentation rate is widely accepted as a diagnostic aid, its normal variation and accuracy, and even its clinical significance, the authors declare, have never been clearly established, particularly in regard to children. In an attempt to remedy this defect the erythrocyte sedimentation rate (E.S.R.) of 293 children aged from 4 to 15 years and judged to be clinically well was determined at the School of Public Health, Berkeley (University of California), by three established techniques, namely, the Wintrobe method, the Westergren method modified by the use of Wintrobe's anticoagulant mixture instead of citrate, and by the micromethod of Landau and Adams, also modified by the use of blood collected into Wintrobe's dry anti-coagulant before diluting with sodium citrate solution in the bulb.

From their own results and a survey of the literature the authors draw a number of conclusions. The E.S.R. at 1 hour for healthy children aged 4 to 15 years ranged from 0 to 20 mm., both by the uncorrected Wintrobe and the Landau-Adams techniques, although about 5 to 10 per cent. of apparently well children may have a rate higher than 20 mm. The younger children, aged 4 to 11 years, had a higher rate (average 12 mm.) than children aged 12 to 15 years (average 7·5 mm.). The authors found that the correlation between the three methods when applied to the same specimen of blood was very high, and they consider that employment of any of these methods would give similar results. The type of anticoagulant used made little difference to the result. However, when thirty estimations were made on one sample of blood, readings at 1 hour were found to vary by ±5 mm. with Wintrobe's method, ±7 mm. with the Landau-Adams microtechnique, and by ±4 mm. with Westergren's method. This variation must therefore be borne in mind when considering the clinical significance of the result when determined by a single technique. They consider that in children correction for anaemia is not necessary, since the correlation between the corrected and uncorrected E.S.R. by the Wintrobe method is extremely high (0·95). The packed cell volume was also determined and was found to increase gradually with the year of age, the average being 40 per cent. in the age group 4-11 and 43 per cent. in the age group 12-15. *R. F. Jennison.*

Study of the Erythrocyte Sedimentation Rate in Metastatic Cancer of the Bones. (Étude de la vitesse de sédimentation dans les cancers secondaires des os.) SÈZE, S. DE, FLAMAND, —., and DESMICHELLE, —. (1953). *Bull. Soc. méd. Hôp. Paris*, **69**, 162. 1 fig.

The authors agree that previous work by various authors on the influence of cancer on the erythrocyte sedimentation rate (E.S.R.) has shown that cancers can be divided into three groups, of which the first (for example, carcinoma of the breast) cause no appreciable change in the E.S.R., even when there is ulceration, the second (tumours of the lung and digestive tract) are usually associated with infection and nearly always with an accelerated E.S.R., while the third, though not infected, invariably give a higher reading; this group comprises tumours of the testicle, ovary, uterus, and kidneys.

In the study here reported the authors determined the E.S.R. in forty cases of metastatic growths of various types in bone, the rate in eighteen cases of Pott's disease and twenty of osteoporosis being determined for control purposes. They found that the rate was constantly and considerably accelerated in cases of carcinoma, the average reading being between 40 and 90 mm. in the first hour; in the cases of Pott's disease the acceleration was of a lower order, while in the osteoporotic cases (with the exception of two cases) the rate was nearly normal. A single metastatic deposit sufficed to raise the E.S.R. (the primary tumour having been removed), and this rise appeared to be independent of the presence of

anaemia or infection. Carcinoma of the prostate gave the highest readings and tumours of the digestive tract the lowest. The finding of normal E.S.R. should, therefore, throw doubt on the diagnosis of metastatic cancer of bone.

[The method of estimation of the E.S.R. is not mentioned, but presumably it was that of Westergren.]

D. Preiskel.

Clinical Value of Eosinophil Counts and Eosinophil Response Tests. BEST, W. R., KARK, R. M., MUEHRCKE, R. C., and SAMTER, M. (1953). *J. Amer. med. Ass.*, **151**, 702.

The revival of interest in the eosinophilic granulocyte, that "beautiful but mysterious cell", has been due to two recent discoveries, that adrenal cortical activity produces eosinopenia, and that the absolute eosinophil count is fairly simply performed and much more accurate than the differential count.

At the University of Illinois College of Medicine eosinophil counts were made using Randolph's stain (0·1 per cent. phloxine in equal parts of propylene glycol and distilled water) and the average of four chambers was taken. The limits of normal (at 8 a.m. in 42 healthy men) were 70 and 450 cells per c.mm. There was a mid-morning fall in the count by about 20 per cent., and an evening rise to about 30 per cent. above the normal 8-a.m. count.

The commonest cause of a rise in the eosinophil count is an antigen-antibody of the anaphylactic type. The authors discuss and give a full list of the causes of eosinophilia and eosinopenia. In the diagnosis of Addison's disease it was shown that if the Thorn test is carried out by giving intravenously over 4 hours 50 units ACTH in 500 ml. of 5 per cent. glucose there will be a profound fall in the eosinophil count after a further 4 hours in those with intact adrenals, and poor response in cases of Addison's disease. The adrenaline-response test was not found to be reliable. Eosinophil counts are useful in ACTH therapy but not necessary during treatment with cortisone. *G. S. Crockett.*

Reproducibility and Constancy of the Platelet Count. BRECHER, G., SCHNEIDERMAN, M., and CRONKITE, E. P. (1953). *Amer. J. clin. Path.*, **23**, 15. 18 refs.

At the U.S. National Institutes of Health the authors investigated the accuracy of platelet counts on venous and capillary blood from thirteen healthy male subjects, using a phase-contrast microscope. Venous blood collected in silicone-coated test-tubes and capillary blood taken direct from a finger was diluted 1 in 100 with a 1 per cent. solution of ammonium oxalate. The platelets were allowed to settle for 15 minutes in a counting chamber with a flat bottom and covered with a No. 1 cover slip. (It is emphasized that a flat-bottomed chamber and a thin cover slip are essential for phase-contrast microscopy.) To prevent drying, the chamber was placed in a Petri dish with a moistened pledget of cotton wool. The platelets are easily recognizable under the phase-contrast microscope, appearing as individual round or oval bodies with a pinkish or purple sheen. Eight counts were made on each sample of venous blood and one on each of eight successive drops of capillary blood from each of the thirteen subjects on four separate occasions during the course of several weeks.

The mean of all counts on capillary blood was 242,000 per c.mm., and of those on venous blood 248,000 per c.mm., the difference of 2½ per cent. being statistically highly significant. Moreover, the variation between individual counts on capillary blood was approximately twice as great as with venous blood, the latter being no more than that calculated to result from errors inherent in the haemocytometer method. These differences between venous and capillary blood are considered to be probably due to dilution of the latter with tissue fluid and to loss of platelets in the puncture wound.

The authors conclude that platelet counts made with the phase-contrast microscope on venous blood collected in siliconed vessels and rapidly diluted with a suitable anticoagulant reflect the circulating platelet level with an accuracy which is dependent only upon the number of counts made on each sample. Other methods of platelet counting are discussed and compared. *Kate Maunsell.*

Agglutination test with Sensitized Sheep's Erythrocytes in the Differential Diagnosis of Rheumatic Diseases. (Der Agglutinationstest mit sensibilisierten Hemmelblutkörperchen in der Differential-diagnose rheumatischer Erkrankungen.) GAMP, A., and GILLISSEN, G. (1953). *Z. Rheumaforsch.*, **12**, 129. 11 refs.

Photographic Method of Recording Red Cell Counts. SWISHER, S. N., and IZZO, M. J. (1953). *J. Lab. clin. Med.*, **41**, 953. 2 figs, 2 refs.

Haemagglutinating Factor in the Blood of Patients suffering from Rheumatoid Arthritis. (Le facteur hémagglutinant dans le sang des malades souffrant d'arthrite rhumatoïde.) SVARTZ, N., and SCHLOSSMANN, K. (1953). *Schweiz. med. Wschr.*, **83**, 782. 6 refs.

Investigations into the Antistreptokinase, Antihyaluronidase, and Antistreptolysin Reactions. (Untersuchungen mit der Antistreptokinase-, der Antihyaluronidase- und der Antistreptolysin-Reaktion.) CHRIST, P. (1953). *Z. Rheumaforsch.*, **12**, 141. 3 figs, 36 refs.

Effect of Large Doses of Congo Red on the Serum Cholesterol Level in Patients with Rheumatism and in Normal Subjects. (L'effetto sul colesterolo sierico di forti dosi di rosso congo in reumatici ed in soggetti normali.) MASONI, A., PELLEGRINI, P., and SCARANGELLA, D. (1953). *Policlinico, Sez. prat.*, **60**, 887. 3 refs.

Outline of the Histogenesis of Rheumatic Lesions. (Esquisse de l'histogénèse des lésions de l'inflammation rhumatismale.) JUSTIN-BESANÇON, L., RUBENS-DUVAL, A., and VILLIAUMEY, J. (1953). *Sem. Hôp. Paris*, **29**, 2003. Bibl.

Streptococcal Antibodies in Rheumatic Disease. (Gli anticorpi antistreptococcici nella malattia reumatica.) BARTOLOZZI, G., and BORGHERESI, S. (1953). *Riv. Clin. pediat.*, **51**, 688. Bibl.

Histopathology of the Kidney in Rheumatic Heart Disease. (Ricerca sistematica di istopatoligia renale in casi di cardiopatie reumatiche.) SACENTI, M. (1953). *Riv. Anat. patol.*, **6**, 625. 12 figs, 34 refs.

Measurement of Protein Balance in Rheumatic Subjects. (A propos de quelques mesures de l'équilibre protidique des rhumatisants.) LACAPÈRE, J., and GAGER, A. (1953). *Rev. Rhum.*, **20**, 483. 13 figs, 4 refs.

Serum Lipoids in Rheumatoid Arthritis. (Die Serumlipoide bei der primär chronischen Polyarthritis.) SCHMID, J., ENZINGER, J., HERBST, F., and WARUM, F. (1953). *Wien. klin. Wschr.*, **65**, 557. 3 figs, 17 refs.

Laboratory Aspects of Rheumatoid Arthritis. (Aspectos de laboratorio en la artritis reumatoide.) LOSADA, M., ZAÑARTU, J., ATRIA, A., ETCHEVERRY, R., CONCHA, E., and ACEVEDO, H. (1953). *Rev. clín. esp.*, **50**, 203. 4 figs, 25 refs.

ACTH, Cortisone, and Other Steroids

Treatment of Psoriatic Rheumatism with ACTH and Cortisone. (Traitement par l'ACTH et la cortisone du rhumatisme psoriasique.) COSTE, F., PIGUET, B., and CAYLA, J. (1953). *Rev. Rhum.*, **20**, 208.

The results of treatment with ACTH or cortisone of seventeen cases of the rather rare psoriatic form of articular rheumatism are discussed. Of the twelve cases treated with cortisone, three failed to respond, the failure of two being possibly due to insufficient dosage. Of the five cases treated from the beginning with ACTH, only one failed to respond, low dosage again being suspected as the reason. However, one of the cortisone-resistant cases responded subsequently to ACTH, and the single ACTH-resistant case improved when cortisone was given. The doses used in the majority of cases were comparable to those employed in the treatment of rheumatoid arthritis, but in a few cases a daily dose of 200 mg. or even 300 mg. of cortisone proved necessary. Both the oral and parenteral routes were employed in the administration of cortisone [but the dosage given orally is stated only in the one case which failed to respond].

The effect of the treatment on the psoriasis was usually first seen between the 2nd and 5th days, when the lesions became paler and began to subside, pruritus disappeared, and desquamation became less intense. Ungual psoriasis invariably improved, but was not eradicated. Only in three cases out of seventeen did the skin lesions fail to respond to treatment, but cessation of treatment, or even a reduction of the dose, was soon followed by a relapse. The effect of the treatment on the arthritis was comparable to that observed in cases of uncomplicated rheumatoid arthritis. *A. Swan.*

Experimental Production of Arthritis in Rats by Hypophyseal Growth Hormone. REINHARDT, W. O. and LI, CHOH HAO (1953). *Science*, **117**, 295. 2 figs, 6 refs.

The experiments described in this paper from the University of California were undertaken to determine the role, if any, of the pituitary growth hormone in the production of chronic arthritis in the absence of the adrenal glands and gonads. Of 38 plateaued [*sic*] female rats, 6 to 8 months old, eighteen were subjected to adrenalectomy and ovariectomy, the remainder serving as controls. Gradually increasing daily doses of pituitary growth hormone were given by intraperitoneal injection to ten rats in each group for a period of 6 months. All the animals were maintained on saline and a stock diet in comparable environmental conditions. At the end of the 6-month period the weight of the animals receiving growth hormone in both groups was 65 per cent. greater than that of untreated normal controls, but the former became sluggish and irritable. Knee and ankle-joints became tender, and there were transient episodes of joint swelling.

Radiographs of all treated animals disclosed joint disturbances, especially at the knee, characterized by irregularities and erosions of the condylar margins, local osteoporotic areas, and lipping and calcification at the joint margins. During the experiments two animals, which were in poor condition, were given hydrocortisone for one week, with apparent improvement.

The significance of these results is briefly discussed. It is pointed out, however, that the evidence provided by the experiments "does not preclude the possible existence of sensitization to growth hormone or of production of hypersensitivity to other allergenic factors". *C. L. Cope.*

Treatment of the Schoenlein-Henoch Syndrome with Adrenocorticotrophic Hormone (ACTH) and Cortisone. PHILPOTT, M. G., and BRIGGS, J. N. (1953). *Arch. Dis. Childh.*, **28**, 57. 2 figs, 5 refs.

At the Children's Hospital, Sheffield, nine patients with the Schoenlein-Henoch syndrome were treated with ACTH and cortisone, six receiving ACTH alone, two ACTH followed by cortisone, and one cortisone alone. Within 48 hours an improvement was observed in the general condition of five of the patients; three improved more slowly. In five of six patients joint swellings and intestinal haemorrhage subsided with treatment. Skin manifestations recurred in eight patients during treatment. Nephritis, present in two patients before treatment, was unaffected; in three this complication developed during, or shortly after cessation of, hormone therapy.

The author concludes that ACTH and cortisone are of no value in the treatment of renal and skin manifestations of the Schoenlein-Henoch syndrome. The action of the drugs in the patients with joint swellings and intestinal haemorrhage was doubtful. It is suggested that only in cases with severe constitutional disturbance should hormone therapy be considered. *J. G. Millichap.*

Temporal Arteritis and its Treatment with Cortisone and ACTH. WHITFIELD, A. G. W., COOKE, W. T., JAMESON-EVANS, P., and RUDD, C. (1953). *Lancet*, **1**, 408. 18 refs.

A diagnosis of temporal arteritis was established in seven women and five men, aged 66 to 83 years, at the United Birmingham Hospitals. Ten of the patients com-

plained of loss of vision, a disability which amounted to complete blindness in four. After a course of treatment with cortisone or ACTH head pains, arterial tenderness, and pyrexia subsided rapidly, accompanied by improvement in the general condition. On the other hand, the erythrocyte sedimentation rate remained high, an indication that the disease was still active. One patient died from coronary occlusion 4 weeks after a course of ACTH therapy, and four patients were found to be suffering from active disease some months after the cessation of treatment. A successful result was obtained in a woman, aged 76 years, whose fundi revealed haemorrhages and arteriosclerotic changes. After a course of ACTH therapy over a period of 42 days there was marked improvement in the visual acuity and visual fields; no evidence of relapse was detected 12 months after treatment ceased.

The authors consider it possible that cortisone therapy was of value in five cases of recent partial loss of vision in this series. There was no improvement in vision in the four totally blind patients or in a patient with long-standing partial loss of vision. Maintenance therapy was considered to be essential in all cases, for relapse occurred when the dosage was reduced. Apparently the treatment controlled the arteritis, and prevented further loss of vision.

The authors recommend that ACTH should be given intramuscularly or by slow intravenous drip, and cortisone by mouth or intramuscularly. [The dose of cortisone is not specified, but the case reports include references to the administration of ACTH in doses of 20 mg. daily for 5 to 14 days.] *A. Garland.*

Effect of Cortisone on the Regeneration of Skeletal Muscle after Injury. SISSONS, H. A., and HADFIELD, G. J. (1953). *J. Bone Jt Surg.*, **35B**, 125. 9 figs, 11 refs.

In experiments carried out at the Institute of Orthopaedics and St. Bartholomew's Hospital, London, it was found that, as with a variety of other tissues, cortisone delayed repair of the muscles of young growing rabbits which had been injured experimentally by crushing. The results were compared in three groups of animals, the first group being given cortisone daily in subcutaneous injections of 10 mg./kg. body weight, the second group 20 mg./kg. body weight, while the third group, not given cortisone, acted as a control.

While a delay in starting regeneration and a slowing down of its progress were clearly established, full regeneration did eventually occur. It thus appears that the effects of cortisone in inhibiting repair processes in muscle are much less than those in bone, the authors having previously shown (*Brit. J. Surg.*, 1951, **39**, 172) that in experimental fractures in animals receiving cortisone there was no evidence of union of the bone fragments as late as 21 days after injury. It seems probable that the different process of repair in these two tissues—by mitotic cell division in bone and by extension of the severed cytoplasmic syncytium in muscle—may explain the difference in the sensitivity of these tissues to cortisone. The authors suggest that the initial delay in regeneration may be due to adrenal hyperactivity as part of a stress syndrome caused by the injury. *L. Michaelis.*

Treatment of Nephrotic Syndrome with Interrupted ACTH or Oral Cortisone Therapy. LANGE, K., SLOBODY, L., and STRANG, R. (1953). *Proc. Soc. exp. Biol., N.Y.*, **82**, 315. 2 figs, 8 refs.

The authors have previously reported persistently low levels of serum complement in all cases of acute and subacute glomerulonephritis, including nephrosis. They consider that this is caused by an antigen-antibody reaction, in the course of which complement becomes fixed. The complement level rises with improvement in the disease, while it falls during a relapse: in one hundred cases without any signs of nephritis the level was 1 to 3 units. Since the authors consider that ACTH and cortisone depress antibody formation, they postulate that the complement level might be affected by these hormones in nephritis.

To investigate this possibility sixteen cases of the nephrotic syndrome at the Metropolitan Hospital, New York, with an average complement level of 0·71 unit, were given 100 mg. ACTH daily for 7 days. Diuresis, preceded by a rise in the serum complement level, resulted in most cases. When a relapse occurred it was associated with a fall in complement level. Some patients receiving as maintenance therapy 100 mg. ACTH on three successive days each week for 5 to 8 weeks showed persistent improvement, the serum complement level remaining within the normal range. Interrupted cortisone therapy produced the same results. The blood chemical picture improved simultaneously with both ACTH and cortisone therapy. *G. Loewi.*

ACTH in Reiter's Syndrome. Four Cases, with Review of the Literature. LARSON, E., and ZOECKLER, S. J. (1953). *Amer. J. Med.*, **14**, 307. 5 figs, 33 refs.

To the three cases of Reiter's syndrome treated with ACTH already reported in the literature the authors add four more which were seen at the Veterans Administration Hospital, Des Moines, Iowa.

The first patient, a man of 24, had a severe attack of Reiter's syndrome which did not respond to administration of salicylates, penicillin, streptomycin, or a non-specific protein; he resisted physiotherapy because of pain and stiffness in the joints. After a course of ACTH in doses of 25 mg. every 6 hours the patient was able to walk, his appetite and general condition improved, and physiotherapy could be carried out satisfactorily. Hospital treatment in this case lasted 7 months. The second patient had an even more severe attack of Reiter's syndrome, which required 15 months' hospital treatment. The authors believe that had it not been for the administration of ACTH physiotherapy in this case would have been impossible and the residual deformity would have been severe. The third patient, who had the most severe attack of Reiter's syndrome, became refractory to ACTH, and marked osteoporosis developed. Physiotherapy, although painful, was persisted in, as was administration of ACTH, and the patient recovered completely, the duration of treatment having been 17 months. The fourth patient, who had a less severe attack than the others had had a short course of cortisone, with temporary relief of symptoms, before admission to hospital. Arthritis

recurred and he was admitted to hospital, where administration of ACTH permitted physiotherapy to be maintained until all joint distress had disappeared.

The authors conclude that ACTH has a definite place in the over-all management of Reiter's syndrome.

James D. P. Graham.

Synergistic Action of Liquorice and Cortisone in Addison's and Simmonds's Disease. BORST, J. G. G., VRIES, L. A. DE, HOLT, S. P. TEN, and MOLHUYSEN, J. A. (1953). *Lancet*, **1**, 657. 6 figs, 14 refs.

The authors have previously shown (*Lancet*, 1950, **2**, 381; *Abstracts of World Medicine*, 1951, **9**, 236) that oral administration of extract of liquorice or of the glycyrrhetinic acid obtained from it has the same effect as treatment with deoxycortone. Continuous therapy with liquorice causes retention of sodium, chloride, and extracellular fluid, while the excretion of potassium is increased. There is a rise in the blood volume and the cardiac output. Later there is an increase in the excretion of water and sodium chloride, and a new equilibrium is reached between intake and output. If at this stage deoxycortone is given in addition it has practically no effect. Cessation of treatment with liquorice causes a "rebound" in which sodium, chloride, and extracellular fluid are lost and potassium is retained. This "rebound" occurs later and also lasts longer than that which develops after cessation of treatment with deoxycortone.

The authors now report from the University of Amsterdam their finding, in treating a case of Addison's disease which did not show the characteristic reactions to treatment with liquorice extract, that in this disease a synergism exists between liquorice and cortisone. When the administration of liquorice, which was given in a dosage of 30 g. daily, was stopped the patient showed no change in the excretion of electrolytes and almost no "rebound". During treatment he became nauseated, had no appetite, and lost weight, but he recovered on receiving 5 mg. of deoxycortone daily. Subsequently the patient was given 40 mg. cortisone daily. There was a moderate retention of extracellular fluid and loss of potassium, and he felt better but continued to lose weight. This treatment was then combined with administration of 15 g. liquorice extract daily, as a result of which the excretion of sodium was approximately halved, the excretion of potassium was increased, and there was retention of water. The blood pressure rose and there was a rapid increase in weight. The dose of cortisone was then reduced to 5 mg. daily while the same dose of liquorice was continued. On this regimen the improvement was maintained, but as soon as the small dose of cortisone was stopped the patient rapidly got worse.

Two other patients with Addison's disease and one with Simmonds's disease were also treated with small doses of liquorice extract and cortisone, with the same results. All four cases are reported in detail.

The authors discuss this remarkable potentiating effect of cortisone on liquorice extract, but are unable to offer any satisfactory explanation for it. *A. C. Crooke.*

Effect of Androgenic Hormones upon the Adrenal Atrophy produced by Cortisone Injections and upon the Anti-inflammatory Action of Cortisone. WINTER, C. A., HOLLINGS, H. L., and STEBBINS, R. B. (1953). *Endocrinology*, **52**, 123. 2 figs, 12 refs.

It has been shown that in the rat exogenous cortisone produces marked adrenal atrophy, together with loss of body weight and atrophy of the thymus. The authors, working at the Merck Research Institute, Rahway, New Jersey, have investigated the effect of the androgenic hormones, methyl testerone and methylandrostenediol (MAD), on this cortisone-produced atrophy. Adrenal atrophy was demonstrated by loss of weight in the gland as compared with controls, and histologically by reduction in size of the adrenal cortex and loss of lipoid substance. Their results showed that adrenal atrophy occurring during cortisone therapy was largely prevented by androgenic hormones, if these were given concurrently. Loss of body weight and thymic atrophy, however, were not prevented.

The adrenals of hypophysectomized rats undergo severe atrophy, and there is also loss of body weight. Cortisone and MAD when given separately are without effect on these changes, but when given simultaneously they restore the weight and histological anatomy of the adrenal gland to almost normal proportions. The effect of MAD was then assessed on the adrenal atrophy shown to occur after about 17 days' treatment with cortisone. Recovery from this atrophy did not occur more quickly in animals treated with MAD than in untreated controls.

Cortisone is well known to inhibit inflammatory reaction induced by chemical and mechanical irritants in the experimental animal. The authors' observations have shown that the androgenic hormones had no effect on this inhibitory action of cortisone. Since the adrenal-sparing action of the androgenic hormones occurs in the hypophysectomized animal, its action is presumed not to be mediated through the pituitary stimulation of production of corticotrophin, but to be a direct one. It is of interest to note that MAD was effective only in conjunction with cortisone.

[Since adrenal atrophy is not a necessary sequel of cortisone therapy in the human patient, the clinical application of this work is not at the moment apparent.]

J. N. Harris-Jones.

Role of the Adrenal Cortex in Fluid and Electrolyte Metabolism. PRUNTY, F. T. G., KAY, H. E. M., LEE, G. DE J., and MCSWINEY, R. R. (1953). *Brit. med. J.*, **1**, 852. 8 figs, 18 refs.

In this paper from St. Thomas's Hospital Medical School, London, the authors discuss the evidence at present available as to the part played by the adrenal cortex in fluid and electrolyte balance as revealed by metabolic studies in human beings. They cite the findings in individual patients as examples.

In adrenal insufficiency the patient is unable to respond to water-loading by a normal diuresis. According to the authors, this can be corrected in cases of Addison's disease or of panhypopituitarism by the previous administration of cortisone, in doses of 100 mg. daily intra-

muscularly, though the volume of urine excreted during the night tends to be diminished by this treatment. The administration of ACTH produced the same effects in cases of hypopituitarism, but not in Addison's disease. The administration of deoxycortone acetate (DCA), as by implantation of 800 mg., did not modify the abnormal response to water-loading, though it restored sodium and chloride losses and maintained hydration.

The administration of ACTH or of cortisone of hydrocortisone (Compound F) to an individual with normal adrenal cortical function usually led to persistent retention of water and sodium, with an increase in weight proportional to the amount of fluid retained. This was demonstrated in a patient with rheumatoid arthritis who was given 25 mg. ACTH intramuscularly every 6 hours. After the dose of the hormone had been reduced or its administration stopped altogether, there was a diuresis, especially of sodium. The authors' observed that oedema may be induced without obvious fluid retention, suggesting that fluid is transferred from the cells to the extracellular fluid. This, they say, can be confirmed by measurement of the extracellular space with inulin and by estimation of chloride balances.

In some cases the retention of sodium may be only transitory; in others a diuresis of water and sodium may occur, either during the administration of ACTH or perhaps to a greater extent after its withdrawal, the latter effect being perhaps due to a sudden relative adrenal cortical insufficiency. In one patient with rheumatoid arthritis there was a persistent loss of sodium and water under the influence of ACTH, and this continued during a subsequent period of cortisone therapy.

Whether a specific "electrolyte hormone" is secreted by the adrenal cortex has not, according to the authors, been established. They find that cortisone and hydrocortisone have many of the properties of deoxycortone. In patients with intact adrenal glands their behaviour is similar: all three hormones cause increased reabsorption of sodium by the kidney, and all may produce retention of water and sodium at first, but sustained treatment either with DCA or with cortisone or hydrocortisone is followed by a spontaneous diuresis. Moreover, patients after total removal of the adrenal glands can be kept in good condition by means of cortisone alone. The effects of administration of these hormones are not, however, identical in Addison's disease. In patients with this disease overdosage with DCA leads to sustained oedema and sodium retention. In one patient the administration of 2·5 mg. daily led to a positive sodium balance, whereas during the administration of 100 mg. cortisone daily by mouth the sodium balance became negative, urine volume and fluid intake increased, and the serum sodium level rose. Moreover, a substance has recently been isolated from the adrenal blood which has far greater effects upon electrolyte metabolism than has cortisone.

The possibility of the intervention of antidiuretic hormone from the posterior pituitary has not been completely elucidated, but the methods of assay of this hormone have recently been criticized, and the authors consider that it is wiser to regard the failure of diuresis in Addison's disease as being due to the lack of glucocorticoid effect upon reabsorption of water from the distal renal tubules.

A working hypothesis is suggested for the effects of adrenal cortical hormones upon water and electrolyte metabolism, as follows. Adrenal cortical hormone leads to an initial retention of sodium and water. At the same time water is transferred from the tissues to the extracellular fluid, the sodium content of which often rises. Loss of water from the tissues accounts for some of the urinary losses of potassium and the resulting fall in the serum potassium level. Expansion of the extracellular fluid leads to an increased water intake and excretion. After the action of the hormone ceases, a large diuresis of water and sodium occurs from the expanded extracellular fluid. *Robert de Mowbray.*

Observations on the Effect of Adrenal Steroids on Vaccinia Virus. Effect of Cortisone in Experimental Vaccinia-Virus Keratoconjunctivitis of the Rabbit. KIMURA, S. J., THYGESON, P., and GELLER, H. O. (1953). *Amer. J. Ophthal.*, **36**, 116. Part 2. 10 refs.

The inoculation was by means of a 6-mm. corneal trephine cut, the blade being wet with a 10^{-1} suspension of standard virus. The conclusions reached confirmed reports of previous workers that the use of cortisone in such cases was not beneficial, that prior use by any route failed to bestow any protection, and that the course of the disease in some cases so treated was more severe than in controls. Encephalitis was observed only in animals given intramuscular cortisone. *P. Jameson Evans.*

Ocular Leprosy successfully treated with Cortisone and Corneal Graft. (Lèpre oculaire traitée avec succès par le cortisone et par une greffe de la cornée.) DEGOS, R., VOISIN, J., and DELZANT, O. (1952). *Bull. Soc. franç. Derm. Syph.*, **59**, 249.

Corneal scars secondary to ocular leprosy were successfully treated with local cortisone and a lamellar corneal graft. Vision improved from light perception to 4/10. A pathological examination of the cornea revealed inflammatory non-specific lesions. *S. Vallon.*

Herpetic Infection, Antihistaminic Drugs, and Cortisone. (Infezione erpetica, antistaminici e cortisone.) BOLES-CARENINI, B., and CIMA, V. (1953). *Boll. Oculist.*, **32**, 413. 25 refs.

Antihistaminic drugs have a delaying and limiting effect on the evolution of experimental herpetic keratitis, whereas cortisone exerts no influence. *G. Cristini.*

Action of ACTH on the Blood-Aqueous Barrier. (L'azione dell'ormone corticotropo ipofisario [ACTH] sulla barriera emato-oftalmica.) SIMONELLI, M., and CALAMANDREI, G. (1952). *Atti Soc. oftal. Lombarda*, **6**, 74.

Five patients were treated with an active ultra-filtrable fraction of corticotropic hypophyseal hormone and one with cortisone in order to assess the action of ACTH on the blood-aqueous barrier; no variation was observed. The authors believe that this result is due to the increase of ascorbic acid in the blood, following the administration of these hormones. *S. Magni.*

Cortisone in the Treatment of Syphilitic Eye Disease. ASHWORTH, A. N. (1953). *Brit. J. vener. Dis.*, **29**, 3. 18 refs.

The effect of cortisone is to control inflammation and exudation. In diseases of the eye it may be used topically as drops (5 mg. in 1 ml. normal saline), as ointment in a lanoline base (10 mg. per g.), or by subconjunctival or retrobulbar injection (10 mg. in 0·4 ml. saline); and systemically in the form of tablets or injections of standard saline suspensions. Topical application is indicated where the anterior segment is affected, and systemic administration where the posterior segment is affected.

The present author reports 28 cases of interstitial keratitis treated at the Royal Eye Hospital, Manchester. Photophobia and pain were rapidly relieved, but the condition showed a marked tendency to relapse if treatment was stopped too early. According to the author, this should usually extend over 3 to 4 months, atropine being used concurrently. He states that it is of the utmost importance in syphilitic cases to give penicillin in large doses at the same time, since cortisone is in no sense curative and may in fact, especially in early cases, encourage the multiplication of treponemes.

In sixteen cases of iridocyclitis not proved to be due to syphilis, treatment with cortisone alleviated the symptoms, but results were better in acute than in chronic cases; relapses were frequent. Results were much the same in six cases of choroiditis treated systemically.

(In the discussion which followed this paper, which was read before the Medical Society for the Study of Venereal Diseases, there was general agreement that cortisone was very valuable, but that it was in no sense curative and must be used in conjunction with penicillin; it was impossible to say how long cortisone should be continued, and instances were given of the other eye being affected after, or even during, treatment of one eye. Some speakers deprecated over-enthusiasm concerning the value of cortisone, but most agreed that it was well worth trying because of its effect in relieving symptoms.)

T. E. Osmond.

Cortisone in Syphilis of the Eye. (1953.) *Brit. J. vener. Dis.*, **29**, 1 (Editorial).

The general principles of treatment with cortisone are briefly reviewed. The hormone is used locally for interstitial keratitis, but systemic administration would be necessary to affect the optic nerve. *J. R. Hudson.*

Cortisone and Ocular Tuberculosis. I. Influence of Cortisone on the Course of Experimental Ocular Tuberculosis in the Normal Rabbit. II. Influence of Cortisone on the Course of Ocular Tuberculosis of the Immuno-Allergic Rabbit. III. Influence of Cortisone on Cutaneous and Ocular Sensitivity to Tuberculin in the Animal infected by general route or by Inoculation in the Anterior Chamber. (Cortisone e tubercolosi oculare. I. Influenza del cortisone sul decorso della tubercolosi oculare sperimentale del coniglio. II. Influenza del cortisone sul decorso della tubercolosi oculare del coniglio immuno-allergizzato. III. Influenza del cortisone sulla sensibilità cutanea ed oculare alla tubercolina dell'animale infettato rispettivamente per via generale ed in camera anteriore.) LEPRI, G., and FORNARO, L. (1953). *G. ital. oftal.*, **6**, 359. 30 figs, 7 refs.

In experimental researches on the rabbit the authors found that cortisone has a slight effect on the course of experimental ocular tuberculosis in the normal animal even if the infection is mitigated by treatment with streptomycin. On the contrary, an almost complete inhibition of the initial allergic reaction in immuno-allergic rabbits followed the administration of cortisone which caused the diffusion of inflammation. The cutaneous and ocular sensitivity to tuberculin was almost completely inhibited during treatment with cortisone. *N. Pagliarani.*

Effects of Liquorice and its Derivatives on Salt and Water Metabolism. CARD, W. I., STRONG, J. A., TOMPSETT, S. L., MITCHELL, W., TAYLOR, N. R. W., and WILSON, J. M. G. (1953). *Lancet*, **1**, 663. 6 figs, 10 refs.

In an investigation at the University of Edinburgh the effect of administration of crude liquorice and of glycyrrhetinic acid was studied in three healthy humans, in a patient with Addison's disease, and in adrenalectomized rats. This treatment was found not to prolong the survival time of the rats, although it led to a gain in weight and retention of sodium and chloride in the healthy subjects and in the patient with Addison's disease. *A. C. Crooke.*

Effects of Cortisone and Desoxycorticosterone on the Toxicity of Barbiturates. GORBY, C. K., LEONARD, C. A., AMBRUS, J. L., and HARRISSON, J. W. E. (1953). *J. Amer. pharm. Ass.*, **42**, 213. 7 refs.

The authors, at the Philadelphia College of Pharmacy and Science, investigated experimentally the effect of cortisone and deoxycortone acetate in barbiturate poisoning. Cortisone acetate given subcutaneously to male Swiss mice in doses of 100 mg./kg. body weight daily for 6 days appeared to offer slight protection from the toxic effects of pentobarbitone sodium injected intraperitoneally on the 6th day in doses below LD_{50}. Similar administration of deoxycortone on the other hand slightly increased the toxic effects of pentobarbitone when it was given in doses above LD_{50}. Both cortisone and deoxycortone, whether administered after the phenobarbitone or throughout a 6-day pre-treatment period, increased the toxic effects of phenobarbitone sodium. Animals died within 5 hours of administration of pentobarbitone, and within 30 hours of giving phenobarbitone.

The reasons for the difference in the effect of cortical hormones are still not known, but the authors consider that during prolonged sleep, factors which might be influenced by the high level of cortical hormones become operative. *I. Ansell.*

Management of Intractable Sprue with Cortisone and Adrenocorticotropin (ACTH). COLCHER, H., DRACHMAN, S. R., and ADLERSBERG, D. (1953). *Ann. intern. Med.*, **38**, 554. 2 figs, 10 refs.

The authors report from the Mount Sinai Hospital, New York, the treatment of eight cases of intractable primary sprue in four men and four women, of whom seven had non-tropical sprue and the eighth tropical

sprue. In seven of the cases previous treatment with vitamins given parenterally and orally, "tween 80", pancreatin, bile salts, plasma, and blood transfusions had given equivocal results. Diarrhoea, loss of weight, and steatorrhoea were present in all cases, and anaemia and other haematological disorders persisted. ACTH was given only to patients in hospital, treatment after discharge being changed to cortisone. The initial dose was 100 mg. daily for both drugs.

A number of complications were seen. Overt tetany occurred in four cases, and was believed to be due to hypochloraemic alkalosis; it could be prevented by the administration of ammonium chloride. Oedema occurring early in treatment sometimes required mercurial diuretics for its control. In all, thirteen courses of cortisone and eight of ACTH were given. Striking clinical improvement in a few days occurred in five patients, and although no change in the haematological findings was noted, the diarrhoea disappeared promptly and there was a substantial increase in weight. In four cases the vitamin-A absorption curve improved. Some degree of clinical remission occurred in all cases, but clinical relapses invariably occurred 1 to 5 weeks after cessation of therapy. No case of resistance to this form of therapy has developed so far, and it is hoped that the improvement can be maintained by continuous administration of small doses of cortisone. *C. L. Cope.*

Local Tissue Reactions to Cortisone and Hydrocortisone (Compound F) in Man. VIII. Studies of Local Therapeutic Effect of Hydrocortisone in Diseases of Skin. GOLDMAN, L., and PRESTON, R. H. (1953). *Arch. Derm. Syph., Chicago*, **67**, 163. 4 refs.

From a study of the local effects of cortisone and hydrocortisone in a series of 460 patients at the University of Cincinnati College of Medicine it was found that there was a definite local, inhibiting, inflammatory reaction in a wide variety of dermatoses, with the exception of the urticaria-angioneurotic-oedema group of cases and some miscellaneous dermatoses. The methods employed and the results obtained are described. The reaction was produced by direct local injection and not by the topical application of an ointment or suspension.

G. B. Mitchell-Heggs.

Effect of ACTH and Cortisone on Cerebral Blood Flow and Metabolism. SENSENBACH, W., MADISON, L., and OCHS, L. (1953). *J. clin. Invest.*, **32**, 372. 13 refs.

Measurements of cerebral circulatory and metabolic functions were made in a series of patients before, during, and after treatment with cortisone and ACTH, and in two patients with Cushing's syndrome. Parallel increases in the mean arterial blood pressure [MABP] and cerebral vascular resistance [CVR] occurred in both the cortisone and ACTH treated patients. The mean cerebral blood flow [CBF] was unchanged. The results are interpreted to mean that the cerebral circulation shares equally in an increase in general peripheral vascular resistance. ACTH and cortisone do not appear to exert a specific, local effect upon cerebral blood vessels. Similar changes in the cerebral circulation, that is, parallel increases in MABP and in CVR, with normal CBF were found in two subjects with Cushing's syndrome. Significant changes in the mean cerebral utilization of oxygen and glucose did not occur during the administration of cortisone or ACTH. Cerebral oxygen and glucose utilization were normal in patients with Cushing's syndrome.

These studies provide no explanation for the mental changes that occurred during the administration of cortisone and ACTH.—[*From the authors' summary.*]

ACTH in Gelatin. Clinical Results with Repository Adrenocorticotropic Hormone in Allergic Diseases. LEVIN, S. J. (1953). *Ann. Allergy*, **11**, 157. 15 refs.

In an investigation of the results of treatment with repository ACTH in allergic diseases at the Children's Hospital of Michigan and the Wayne University School of Medicine, Detroit, Michigan, 37 allergic patients, sixteen of whom were suffering from severe asthma, were given ACTH in gelatin intramuscularly. Usually 40 to 60 mg. was given daily for the first 2 days, then 20 to 40 mg. on the 3rd day, and 20 mg. if necessary on each of the 4th, 5th, and 6th days. Treatment was then discontinued without further tailing off. This form of treatment was used to transform the severe character of the allergic state into a milder form, and was followed by the routine methods of anti-allergic treatment.

Local or general side-effects were absent, and the therapeutic effect was classed as either "excellent" or "good" in all cases. *H. Herxheimer.*

Prolonged Treatment of Bronchial Asthma with Cortisone. LOWELL, F. C., SCHILLER, I. W., LEARD, S. E., and FRANKLIN, W. (1953). *J. Allergy*, **24**, 112. 7 refs.

At the Evans Memorial Hospital, Boston, Massachusetts, nineteen patients suffering from bronchial asthma of varying severity were treated with cortisone for a year or more. The vital capacity and the rate of expiratory flow were recorded. In seven patients the asthma was of long standing and so severe that it required admission to hospital; in two of these patients the asthma disappeared completely and remained absent under maintenance doses, while in two others occasional intermittent wheezes, which were easily relieved by conventional means, remained present. In a fifth case there was much improvement, although the asthma continued to interfere to some extent with sleep and normal activities. In the last two cases there was initially considerable improvement which, however, could not be maintained in spite of high maintenance doses. In ten other patients the severity of the asthma precluded gainful occupation or housework; in three of these the asthma remained absent under treatment, and in the remainder it was limited to transient wheezes.

The vital capacity returned to normal in seven patients out of the nineteen, but expiratory speed was reduced in most of these. The maintenance dose was 50 to 150 mg. cortisone per day; in the seven very severe cases the mean dose was 121 mg. per day. The appetite was increased in most patients, and body weight increased in ten of them. Hypertension developed in three cases, and rounding of the face in six. Oedema of the ankles was occa-

sionally seen in the early stages of treatment, but was minimal later on. None of the patients had a history of peptic ulcer; in two there was radiological evidence of healed pulmonary tuberculosis, but no evidence of renewed activity. In two patients who sustained accidental fracture of the arm during the course of treatment, healing took place normally.

The results of histamine-inhalation tests were positive in the two patients on whom they were carried out after maintenance doses of cortisone had been given for eighteen months. Intercurrent respiratory infections were difficult to recognize during cortisone treatment, because fever and the usual subjective sensations were slight or absent; however, it was noted that the asthma became worse during the course of such infections even when the dose of cortisone was 150 or 200 mg. per day.

[The very satisfactory result of cortisone treatment and long-term maintenance in these nineteen cases, mostly severe, should be stressed. The observations of the authors are in many details similar to those of the abstracter.] *H. Herxheimer.*

Role of Cortisone in the Treatment of Severe Bronchial Asthma. BURRAGE, W. S., and IRWIN, J. W. (1953). *New Engl. J. Med.*, **248**, 679. 10 refs.

The authors report, from the Massachusetts General Hospital (Harvard Medical School), satisfactory results obtained with cortisone in treating patients in status asthmaticus and resistant to other treatment, patients with severe pollen asthma persisting in spite of pollen hyposensitization, and patients with intractable asthma in whom a specific aetiology had not been established. Cortisone was given only after failure to respond to routine anti-asthmatic treatment for 48 hours in hospital, or in emergency to patients who were critically ill. The dosage may vary considerably with the individual patient. In severe cases of status asthmaticus the oral or intramuscular dosage recommended is 75 mg. every 6 hrs for the first day, then 50 mg. 6-hrly for the second day, followed by 25 mg. 6-hrly until the asthma is controlled.

Most of the authors' patients became symptom-free in 5 to 7 days. It was found that the use of a larger dosage at first to produce complete relief made maintenance treatment with smaller doses easier.

In one patient who died, cortisone having proved ineffective, the smaller bronchioles were found to contain tenacious mucus plugs. It is concluded that cortisone may be a valuable drug in selected cases of severe bronchial asthma, but strict supervision during treatment is essential for success. *J. Pepys.*

Effect of Corticotropin (ACTH), Dihydrostreptomycin, and Corticotropin-Dihydrostreptomycin on Experimental Bovine Tuberculosis in the Rabbit. BACOS, J. M., and SMITH, D. T. (1952). *Amer. Rev. Tuberc.*, **67**, 201. 7 figs, 25 refs.

It was found that corticotrophin did not greatly reduce the resistance of animals previously sensitized to tuberculosis, and that the drug could be administered with safety if dihydrostreptomycin was given simultaneously. *Kenneth Marsh.*

Stevens-Johnson Syndrome treated with ACTH. CALDWELL, W. G. D. (1953). *Lancet*, **1**, 1127. 25 refs.

Cortisone and Rheumatism. (Cortisona y Reumatismo.) CUATRECASAS, J. (1953). *Rev. argent. Reum.*, **17**, 250. 1 ref.

Our Experience with Cortisone in Chronic Inflammatory Rheumatism. (Notre expérience de la cortisone dans les rhumatismes chroniques inflammatoires.) MANTHA, L. (1952). *Un. méd. Can.*, **81**, 1156.

Bronchial Asthma, Rheumatoid Arthritis, and the Connective Tissue Diseases. Treatment with Cortisone and ACTH. HORWITZ, M. (1953). *S. Afr. med. J.*, **27**, 213. 12 figs, 1 ref.

Use of Hydrocortisone Acetate by Intra-Articular Injection for a Variety of Orthopaedic Conditions. SACKS, S. (1953). *S. Afr. med. J.*, **27**, 224. 1 ref.

Temporo-Mandibular Arthralgias and Facial Neuralgias. Treatment with Hydrocortisone Acetate. BROWN, L. (1953). *S. Afr. med. J.*, **27**, 226.

Lack of Cortisone Effect in the Early Stages of Inflammation and Repair. LATTES, R., BLUNT, J. W., ROSE, H. M., JESSAR, R. A., VAILLANCOURT, DE G., and RAGAN, C. (1953). *Amer. J. Path.*, **29**, 1. 20 figs, 8 refs.

Nature, Pathogenesis, and Classification of the Rheumatic Diseases. (Begriffsbestimmung, Pathogenese und Systematik der rheumatischen Erkrankungen.) MOLL, W. (1953). *Praxis*, **42**, 178. 32 refs.

Cortisone combined with Ascorbic Acid in the Treatment of Rheumatoid Arthritis. (Association de cortisone et d'acide ascorbique dans l'arthrite à forme rhumatoïde.) ROUSSEAU, J. (1953). *Laval méd.*, **18**, 581.

Experiences with the Clinical Employment of Cortisone and ACTH. BRØCHNER-MORTENSEN, K., and FISCHER, F. (1953). *Acta med. scand.*, **145**, 97. 8 figs, 16 refs.

ACTH-Like Effect of Acetylsalicylic Acid. BÖE, J., and STÖA, K. F. (1953). *Acta Endocr., Kbh.*, **12**, 201. 4 figs, 10 refs.

Clinical Research into the Mode of Action of Anti-Rheumatic Drugs and their Possible Use in studying Adrenal Function. (Ricerche cliniche sul meccanismo d'azione degli antireumatici e possibile loro impiego nello studio della funzione surrenalica.) BALDUINI, M., and PICCINELLI, O. (1953). *Rif. med.*, **67**, 237. 27 refs.

Study of Adrenocortical Function in Healthy Children after Administration of Sodium Salicylate. (Indagini sulla funzionalità cortico-surrenale in bambini sani sottoposti a somministrazione di salicilato di sodio.) MARTONI, L., and TESCOLA, F. (1953). *Clin. Pediat., Bologna*, **35**, 3. 36 refs.

Influence of ACTH on the Tuberculin Reaction in Rheumatism and Spondylitis. (Die Beeinflussung der Tuberkulinreaktion des Rheumatikers und Bechterew-Kranken durch das adrenocorticotrope Hormon des Hypophysenvorderlappens ACTH.) PFEIFFER, E. F., and WEIDMANN, S. (1953). *Z. ImmunForsch.*, **110**, 82. 21 refs.

Observations on Fifty Cases of Joint Disease treated with Hydrocortisone. (Considerazioni sopra cinquanta artropatie trattate con idrocortisone.) ROBECCHI, A., and CAPRA, R. (1953). *Minerva med., Torino*, **44**, 997. 14 refs.

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Intravenous Use of ACTH in Rheumatic Pneumonitis. CHANCEY, R. L. (1953). *U.S. armed Forces med. J.*, **4**, 1129. 4 figs, 16 refs.

Prolonged Treatment of Rheumatic Disease, and of Cardiac Rheumatism in particular, with Cortisone. (Le traitement prolongé de la maladie rhumatismale, et du rhumatisme cardiaque en particulier, par la cortisone.) VILLA, L., BALLABIO, C. B., and SALA, G. (1953). *Schweiz. med. Wschr.*, **83**, 806.

Experimental Myocarditis induced by Desoxycorticosterone. (La myocardite expérimentale par la désoxycorticostérone (Étude histologique at biochimique).) JUSTIN-BESANÇON, L., RUBENS-DUVAL, A., VILLIAUMEY, J., and HAZARD, J. (1953). *Sem. Hôp. Paris*, **29**, 1994. 16 figs.

Action of Hydrocortisone Acetate on the Articular Exudate. (L'azione dell'acetato di idrocortisone sull'essudato articolare.) BALLABIO, C. B., SALA, G., and BONOMO, E. (1953). *Reumatismo*, **5**, 259. 4 figs, 23 refs.

Adrenal Cortex and Experimental Articular Lesions. (Cortex surrénal et lésions articulaires expérimentales.) JUSTIN-BESANÇON, L., RUBENS-DUVAL, A., VILLIAUMEY, J., and KAHN, J. (1953). *Sem. Hôp. Paris*, **29**, 1987. 8 figs.

Local Action of Steroid Hormones on the Structure and Functions of the Connective Tissue. (L'action topique des hormones stéroides sur la structure et les fonctions du tissu conjonctif.) JUSTIN-BESANÇON, L., RUBENS-DUVAL, A., and VILLIAUMEY, J. (1953). *Sem. Hôp. Paris*, **29**, 1998. 3 figs.

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Information provided by the Estimation of Urinary Cortisonoids in Rheumatism. (Renseignements fournis par le dosage des cortisonoides urinaires chez les rhumatisants.) COSTE, F., DELBARRE, F., and NOZAIS, M.-T. (1953). *Rev. Rhum.*, **20**, 217. 3 refs.

Modified Method for estimating 17-Hydroxy-Corticosteroids in Plasma. BAYLISS, R. I. S., and STEINBECK, A. W. (1953). *Biochem. J.*, **54**, 523. 18 refs.

Other General Subjects

Treatment of Acute Hemophilic Hemarthrosis. A Report on the Use of Hyaluronidase. MACAUSLAND, W. R., and GARTLAND, J. J. (1952). *New Engl. J. Med.*, **247**, 755. 8 figs, 37 refs.

Although haemophilic haemarthrosis is a rare condition, it causes severe pain and results in chronic deformity from contractures and secondary arthritis. The problem is to provide effective early treatment. The authors, at the New York Orthopaedic Hospital, have given hyaluronidase by intra-articular injection; hyaluronidase depolymerizes hyaluronic acid, thus reducing the viscosity of synovial fluid, and also increases the permeability of the synovial membrane. A small quantity of haemorrhagic fluid is aspirated from the affected joint and replaced by 4 or 5 ml. hyaluronidase (equivalent to 1,000 turbidity-reducing units) mixed with 1 per cent. procaine. This is followed by compression of the joint with rest. In some cases a second injection is given after 24 hours. The results in six cases (thirteen joints) were very encouraging in the relief of pain, improved range of movement, and reduction of distension.

[It seems clear that this method is worth further trial.]

Norman Capener.

Animal Experiments on the Pathogenesis of Rheumatism. (Tierexperimentelle Untersuchungen zur Pathogenese des Rheumatismus.) DITTMAR, F. (1953). *Z. ges. inn. Med.*, **8**, 209. 2 figs, 16 refs.

Studies of the Different Pharmacological Effects of Various Anti-Rheumatic Drugs. (Studie über die unterschiedliche pharmakologische Wirksamkeit moderner Antirheumatika.) ZINNITZ, F. (1953). *Münch. med. Wschr.*, **11**, 322. 2 figs, 49 refs.

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